Society of University Surgeons

Vol. 28 AUGUST, 1950 No. 2

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Book Reviews

Urological Aspects of Spinal Cord Injuries. By G. C. Prather. Pp. 146, with 38 illustrations. Springfield, Ill., 1947, Charles C Thomas, Publisher. $3.75.

This little book should be read with care by any physician who has to care for one or more patients with vesical dysfunction due to lesions of the nervous system (not just to traumatic lesions). It deals quite exhaustively with the subject, beginning with detailed discussions of the anatomy, innervation, physiology, and pharmacology of the bladder, and goes on to cover the effects of trauma to the spinal cord upon the bladder, upper urinary tract, and upon the sexual functions in the male. Complications, treatment, and results are discussed exhaustively, and there is a large bibliography. It will amply repay careful reading and study.

Posttraumatic Epilepsy. By A. Earl Walker, Professor of Neurological Surgery, The Johns Hopkins University, Baltimore, Md. Pp. 86. Springfield, Ill., 1949. Charles C Thomas, Publisher.

This is a small book of less than seventy pages of text. The type is large and the illustrations are well reproduced. It is a very readable little book. In spite of its brevity, it contains all essential information on posttraumatic epilepsy. The literature is extensively reviewed and the author's experience in treating 246 posttraumatic epileptics is reported. Neurologists will find information on how to select patients for surgery and what can be accomplished by surgery for posttraumatic epilepsy. Neurosurgeons who are not experienced in surgery for epilepsy will find the technique well described and illustrated.

Nursing Care of Neurosurgical Patients. By Roland M. Klemme, M.D., F.I.C.S., F.A.C.S., Professor of Surgery, Saint Louis University School of Medicine, Saint Louis, Mo. Pp. 142, with 62 illustrations, 1 plate in full color. Springfield, Ill., 1949, Charles C Thomas, Publisher.

This is an excellent book. It is designed primarily for nurses, but all persons interested in the operative and ward care of neurosurgical patients could profit by reading it. Dr. Klemme has restricted the opinions expressed in the book to those held by himself, and, whereas this has permitted greater brevity, it should be appreciated by readers that a certain flexibility of these opinions may exist among neurosurgeons.

Included in the book are chapters on neuroanatomy, signs and symptoms of neurological diseases, neurosurgical diagnostic procedures, and operative technique. There is also a chapter on material and supplies contained on the neurosurgical scrub nurse's table. The chapters are comprehensive and fulfill the author's intent to point out the basic fundamentals in nursing care of these patients.

The 1948 Year Book of Neurology, Psychiatry and Neurosurgery. By Hans H. Reese, Professor of Neurology and Psychiatry, University of Wisconsin Medical School; Nolan D. Lewis, M.D., Director of the New York State Psychiatric Institution and Hospital; Percival Bailey, M.D., Professor of Neurology and Neurological Surgery, University of Illinois. Pp. 75. Chicago, 1948, The Year Book Publishers, Inc.

The purpose of the Yearbook is to give a broad, general survey of the current literature in psychiatry, neurology, and neurosurgery. This volume is well planned and edited. The

abstracts are clear and brief, but include the essential parts of the original article. The editorial comments often added greatly enhance the value of the book.

The Yearbook is of value to and should be read by all physicians interested in remaining abreast with current neurological, neurosurgical, and psychiatric literature.

On the Contributions of Hugh Owen Thomas, Sir Robert Jones, John Ridlon to Modern Orthopedic Surgery. By H. Winnett Orr, with a supplement on Ridlon and His Share in Moulding Orthopedic Surgery by Arthur Steindler. Pp. 253 with illustrations. Springfield, Ill., 1949, Charles C Thomas, Publisher. $4.50.

This small compendium of the essence of the teachings of Hugh Owen Thomas as propounded by himself, his nephew Sir Robert Jones, and his leading American advocate, John Ridlon, reveals a great deal about its author, Dr. Orr. Orr's great contribution to traumatic and orthopedic surgery, the "closed" method of treating osteomyelitis and infected fractures, is a studied application of Thomas' principle of absolute rest to a specific problem. Orr readily acknowledges his debt to the old master and with meticulous care illustrates the contributions Thomas' ideas have made to modern surgical practice by numerous quotations from his work. This is a very personal book, written with a bit of nostalgia. It is a very timely book, re-emphasizing a basic principle in surgery. It is a very interesting book, studded with personal anecdotes and behind-the-scene glimpses into this history of American orthopedics.

Such a book can be read by any surgeon with profit. For the orthopedist, it is a "must."

ANNOUNCEMENT

Plastic Surgery Award

The Foundation of the American Society of Plastic and Reconstructive Surgery offers as its 1950 award $500 (first prize of $300, second prize of $200) and a Certificate of Merit for essays on some original unpublished subject in plastic surgery.

Competition shall be limited to residents in plastic surgery of recognized hospitals and to plastic surgeons who have been in such specific practice for not more than five years.

The essay awarded first prize will appear on the program of the forthcoming annual meeting of the American Society of Plastic and Reconstructive Surgery, to be held in Mexico City, Nov. 27 to 29, 1950. Essays must be in before Aug. 15, 1950.

For full particulars write the secretary, Dr. Clarence R. Straatsma, 66 East 79th Street, New York, N. Y.

Erratum

On page 939 of the June, 1950, issue, in the title of the article "A Rare Case of Bacillus Pyocyaneus (Pseudomonas Aeruginosa) Pyoarthrosis of the Knee," the senior author's name should be spelled "Peter L. Carnesale."

SURGERY

VOL. 28 AUGUST, 1950 No. 2

Original Communications

Society of University Surgeons

RESIDENT TRAINING AND SPECIALIZATION IN SURGERY

S. W. MOORE, M.D., NEW YORK, N. Y.

IT IS particularly appropriate that the Society of University Surgeons should meet in Philadelphia, where Dr. John Morgan was instrumental in founding the first American medical school in 1765, almost 200 years ago.

In his opening "Discourse Upon the Institution of Medical Schools in America," Dr. Morgan uttered these prophetic words: "Perhaps this medical institution, the first of its kind in America, though small in its beginning, may receive a constant increase of strength, and annually exert new vigor. It may collect a number of young persons, of more than ordinary abilities, and so improve their knowledge as to spread its reputation to distant parts. By sending these abroad duly qualified, or by exciting an emulation amongst men in parts and literature, it may give birth to other useful institutions of a similar nature, or occasional rise, by its example, to numerous societies of different kinds, calculated to spread the light of knowledge through the whole American continent, wherever inhabited."

It was just 20 years ago, on my first visit to Philadelphia, that my cousin, Dr. John Gibbon, then professor of surgery at Jefferson Medical College, took me into the yard and showed me the cornerstone of the Pennsylvania Hospital and the date 1755. (Incidentally, Benjamin Franklin was president of the Board of Managers.) This is the oldest institution intended solely for the care of the sick and wounded within the limits of what is now the United States. Temporary buildings had been used since 1752. You in Philadelphia have reason to be proud.

Prior to the foundation of medical schools in North America, it was customary for young men with means to go abroad to study in the schools of Edinburgh, London, or on the continent. Those without the means would apprentice themselves for a term of years to some local practitioner of repute.

It has been estimated that at the onset of the War for Independence, there were upwards of 3,500 practitioners of medicine in the colonies, of which not more than 400 had received medical degrees.

Presidential address at the meeting of the Society of University Surgeons, Philadelphia, Pa., Feb. 9-11, 1950.

In 1758, William Smith, in his *History of New York,* wrote: "A few physicians among us are eminent for their skill. Quacks abound like locusts in Egypt, and too many have been recommended to a full practice and profitable subsistence; this is less to be wondered at, as the profession is under no kind of regulation. Loud as the call is, to our shame be it remembered, we have no law to protect the lives of the King's subjects from the malpractice of pretenders. Any man, at his pleasure, sets up for Physician, Apothecary, and Chirurgeon. No candidates are either examined, licensed, or sworn to fair practice."

During this period, for those fortunate to live in Philadelphia, Boston, or New York, there were systematic courses of lectures and demonstrations. Dr. William Shippen, later to become professor of anatomy and surgery at the Medical School in Philadelphia, started a lecture course in anatomy in 1736, which, for the first series, had 10 students, but in subsequent years had as many as 250 students in a class. There was much opposition to dissection of the human body and several times the building in which the dissections were held was attacked, and more than once the good doctor was forced to evacuate in the face of the enemy.

The first medical school was founded by Dr. Morgan, with his chief associate being Dr. Shippen. It is interesting that in the letter by Thomas Penn, presenting the subject to the Board of Trustees of the College of Philadelphia, Dr. Morgan is given credit for the proposal. Thomas Penn wrote: "He (Morgan) thinks his scheme, if patronized by the trustees, will at present give reputation and strength to the institution, and though it may for some time occasion a small expense, yet after a little while it will gradually support itself, and even make considerable addition to the Academy's funds."

I would like, here, to quote from Dr. Conant's 1949 "President's Report to the Board of Overseers of Harvard University": "Every university which includes a school of medicine is in more or less serious trouble financing this portion of its activities. Harvard is no exception. The factors which have led to the present serious crisis in medical education in the United States are obvious."

The School of Medicine at Pennsylvania was opened in 1765, and in 1768 the first class was graduated with 10 men receiving degrees. To date, 18,353 men have graduated from this school of medicine.

The Medical School of Kings College, New York, later to become the College of Physicians and Surgeons of Columbia University, was the second school to open. This was done in 1768.

Harvard College, the oldest college in the United States, was founded in 1638, but it was not until 1782 that the Medical School was added, due largely to the efforts of Dr. John Warren.

Dr. Conant says, "It is clear there is no such thing as a typical American university, for diversity as to origins, organization, curricula, and means of support are clearly manifest."

However, with the opening of Johns Hopkins in 1893, we entered into a completely new era of American surgery.

Dr. Halsted, as professor of surgery, constituted one of the big four. Although trained in New York at New York Hospital and Bellevue Hospital he traveled extensively in Europe and, before going to Hopkins, came under the influence of the German school. The vigorous young German empire was creating its last cultural achievement. In the generously supported, highly organized, and academically fine state university with its wonderful laboratories, scientific research was bursting with energy. The fundamental discoveries of the new science of bacteriology and the rapidly growing physiology and microscopy were integrated with clinical medicine and soon placed German medicine in the front. Halsted came to know many of these leaders intimately and each year thereafter returned and made new friends.

Until this time, in America a surgeon's training was a matter of personal will, ability, and practical opportunity. A few hospitals offered 1 or 2 years internship culminating as house surgeon. Very little was done in the way of formal teaching and those who got ahead did it on their own by individual work and study. With this type training, some master surgeons educated themselves, but at times, I fear, at the expense of the patients.

The fault of training at that time, and it continues in many places today, began at the bottom and continued to the top. In his short period of 1 to 2 years, the intern suffered not only from inexperience, but also from overexperience. He became accustomed to act without preparation, he acquired a confidence in himself and a self-complacency which, although useful in time of emergency, tended to blind him to his inadequacy and to warp his career.

Halsted was impressed with the contrast between the German and American systems. In the harshly competitive and exceedingly selective system of the German school, the goal was the creation of future teachers. As always, champions beget champions, and great surgeons literally bred great surgeons.

The resident system, as we know it, was fashioned by Halsted on the German model. At the bottom of the pyramid were the interns chosen from the top men of their class, then assistant residents of varying years of service. At the top, or apex, was the resident surgeon, who had usually served 6 years following graduation before attaining this position.

This system, which required so many years to complete, was designed to start with the best, then by word and example, to stimulate mental activity and gradually give responsibility as the surgeon advanced until, as resident, he had assumed complete responsibility for the service.

How do we propose to let the young man spend this time? Service upon the teaching pavilions furnishes the most concentrated surgical training. Here the interns learn to do a "work-up" on patients, outline their pre- and postoperative care, and assist in the operating rooms. The assistant residents help with this work and do a large portion of the operations. It is here that the resident has complete responsibility and does the majority of the major surgery.

On the private pavilions, the training of the resident staff is dependent in large measure upon the senior staff. It is desirable to come in contact with private patients, but this should not constitute the major part of the time spent, as is true in some of our larger clinics where the young surgeon has almost no

actual operative experience on his own responsibility. The ideal is for the assistant resident to work with the senior man on both pavilion and private patients.

It is particularly desirable to have the assistant residents and interns rotate through the specialties in order to form a first hand experience of these conditions, many of which they may be called upon later to care for. This will be discussed in detail later.

Early in the training should come experience in the accident room, where traumatic and acute surgical conditions are first seen, fractures are cared for, and the assistant resident gains experience pertaining to those conditions treated on an ambulatory basis in the outpatient department. It is most important for the resident surgeon to maintain contact with this department in order to follow his operative results and make certain that patients are readmitted at the proper time for stage procedures.

I have said little about anatomy and pathology. These are much more stable than physiology, bacteriology, and biochemistry, which continue to move ahead by leaps and bounds. In the latter group, it is the new which is important and what was written yesterday is almost history today. It is essential to have continuing instruction in anatomy with available cadavers and if possible, fresh material for dissection.

Surgical pathology is an important component of the complete surgical training. The surgical teacher must know both gross and microscopic pathology. In this way, he is able to know not only the help he can obtain from the pathologist but also the limitation in this aid.

The American pathologist is entirely different from his European brother in that he depends almost entirely upon the microscope for his diagnosis, while the pathologist of the old German school relies on his gross examination and rarely resorts to the microscope. There is no substitute for training in gross pathology in the post-mortem room, as well as at the operating table. How many times have we seen a surgeon remove a bit of material for biopsy which gives the pathologist none of the real involved tissue? An inexperienced men cutting blocks for sections may not recognize a small lesion of the liver suspected of being a small single metastasis removed by radical resection. With these errors, the microscopic pathologist is able to offer little aid.

In order to train surgical teachers and leaders, it is essential to develop an investigative spirit in the resident staff. It is true that not all will be productive, but we should attempt to lead the men, by mental stimulation, into clinical research. There is nothing which shows the value of good records and an efficient follow-up system as reviewing a surgical problem with the help of case records.

Original investigation in the experimental laboratory is most valuable, but little can be obtained by forcing an individual who does not have the ability or interest to pursue investigative problems to spend a year in this way. Here, new techniques and operative procedures can be worked out. Tremendous progress has been made by carrying problems to the experimental laboratory and

back to the patient for trial. In no field is this more evident than in recent advances in cardiovascular surgery.

Clinical research can be carried on while the patients are being cared for, but, with the pressure of present-day standards, it is hard for the resident staff to do investigative work in the laboratory at the same time. It seems desirable to give the assistant resident a full-time job there for, say, 1 year. With this background, he may carry on his problems as resident. Certainly after completion of the residency, there will be ample time to further develop this phase of his training should he so desire.

With tremendous strides on all sides, particularly in physiology, biochemistry, and bacteriology, it is necessary to have many clinicians with the ability and desire to recognize clinical problems which may be attacked in the laboratory and, with help from men in other fields, bring them to a successful conclusion.

It was Dr. Halsted's idea to develop a system to produce not only surgeons, but surgeons of the highest type, men who will stimulate the first youths of our country to study surgery and to devote their energies and their lives to raising the standard of surgical science.

How well did he succeed? Schools of surgery which grew up bear the unmistakable stamp of Halsted. We all know the contributions he made to surgical technique. His influence cannot be better measured than to review the careers of those men who worked with him as surgical resident. Harvey Cushing made an imprint on American surgery second only to Halsted. Going to Boston in 1912 to the new Peter Bent Brigham Hospital, he was the first of Halsted's residents to initiate resident training of his own. George Heuer went to Cincinnati and later to New York. He organized resident systems in Cincinnati General Hospital and New York Hospital.

In 1938, the Society of University Surgeons was organized. At that time there were 10 honorary members, representing 10 member hospitals with recognized resident systems, and 59 charter members, each of whom had served for 1 year as resident surgeon. Today, this has grown until there are 26 member hospitals and 203 members.

At this point, I would like it in the record that by 1944, 55 per cent of the active members of the Society were on active duty with the armed forces. In addition, many of the senior as well as honorary members were represented. Other active members came on active duty after 1944.

In the United States, there are 71 approved medical schools. In 32 of these schools, the chairman of the department of surgery is a member of this organization. I think we can agree that resident training is carrying on.

SPECIALIZATION IN SURGERY

In early American medicine there were few doctors, and these were scattered. It was necessary that each physician be self-sufficient. He treated all conditions. With increase in population, there was an increase of doctors and an increase in knowledge. Each man did not have the same interest and, with more medical men in the same community, it was possible for some to develop their special interests. As these interests caused them to probe deeper, their

knowledge in these fields grew. They turned to writing to let others know what they had learned and what they thought. As more and more doctors developed special interests, it became impossible for one man to keep abreast of everything. He then turned with special problems to those men whom he thought best qualified to help. Thus the specialties developed.

Obstetrics was the first field to be invaded by specialists. In colonial times, this was largely in the hands of midwives, although there were eminent men who were distinguished for their skill in obstetrics. In this group, we find William Shippen, Jr., of Philadelphia, who held the chair of professor of anatomy, surgery, and midwifery. The first school in this country to have a professorship devoted solely to midwifery was Kings College (later Columbia), in New York. This chair was created when the college was organized in 1767. Obstetrics has been associated in various schools and varying periods with gynecology and pediatrics.

Marion Sims was responsible for the founding of Woman's Hospital, in New York, which opened in 1855. For years this was the only special hospital in the world for diseases of women. In 1868, the American Journal of Obstetrics began publication. The American Gynecological Society was founded at a meeting of the Academy of Medicine of New York in 1876.

In the development of surgical specialties, it has often been the invention or introduction of a special instrument which separated that field and advanced it. The Sims speculum made it possible for Marion Sims to first operate for vesicovaginal fistula in 1845.

Helmholtz, in 1851, invented the ophthalmoscope, which was of the greatest importance in advancing the field of ophthalmology. Books had appeared on diseases of the eye as early as 1823. There was a growth of special eye hospitals. Developing side by side with ophthalmology we find otology, and most of the early pioneers combined the two specialties.

Coming in this way, there is no definition and no boundary as to what constitutes a speciality. Each man who sets himself up as a specialist pushes the boundaries by his own force, initiative, and ability to cover as much as he desires. With this, there is complete chaos as to terminology as well as boundaries. In the beginning, specialization connoted a man with special knowledge, something in addition to that which all had in common. Now it means more one who limits himself to a special type of disease or a particular anatomic part of the body. Often he has less knowledge than one who has not specialized. We can say a specialist has special ability and special disability.

Until 1917, there were no specified qualifications in any specialty and it was impossible to know who was qualified. In order to meet this need, the specialty boards were organized.

In 1908 it was specifically recognized by some ophthalmologists in this country that the existence of unqualified men in their ranks lowered the standards of the entire specialty. Several factors were involved: one, the growth of optometry; another, the ease with which physicians could label themselves ophthalmologists after spending a few weeks or at most a few months in a post-

graduate course here or abroad. With the approval of the American Ophthalmological Society and the Section of Ophthalmology of the American Medical Association, an examining board was approved in 1915, later called the American Board of Ophthalmology. This was incorporated two years later in 1917.

To date, examining and certifying boards in 19 specialties have been approved by the Council on Medical Education and Hospitals of the American Medical Association. By July 1, 1949, a total of 40,519 certificates had been awarded.

At first the specialty boards were a light in the darkness, but came the subspecialties, the subsidiary boards, and the special certification—and the light grew dim. For example, the American Board of Otolaryngology issues a limited certificate in endoscopy to an exceptionally qualified person. To date, 2 such certificates have been awarded.

In addition to the 19 specialties just mentioned, we have many others in surgery which are being pushed: cancer surgery, vascular surgery, pediatric surgery, geriactric surgery, and where do they end!

It is impossible to define or delineate a surgical specialty. Some confine themselves largely to anatomic regions, others to physiologic systems. Thus we may find the neurological surgeon limiting himself to the brain and spinal cord or he may in addition chase the sympathetic nerves through the chest and abdomen and the peripheal nerves to the tips of the fingers and toes. With the same reasoning, the vascular surgeon invades the chest, abdomen, extremities, and no doubt sometimes the skull also. In certain Army institutions, the hospital regulations define orthopedic surgery as caring for disease and injury of bones, joints, muscles, nerves, and blood vessels. There is no question of the need of a benevolent dictator in a hospital. For example, will the thoracic surgeon care for all surgical diseases in the thoracic cavity, or will it be invaded also by the neurosurgeon, cardiac surgeon, vascular surgeon, gastrointestinal surgeon, as well as the general surgeon? I was once asked, "In case you had a broken leg, would you prefer to have it cared for by an orthopedic surgeon, or by a general surgeon?" I replied that I would prefer to have it cared for by one who was capable of caring for a broken leg.

In certain institutions, men are taken immediately from medical school for training in gynecology and obstetrics. After spending the required time, they are certified by the board as gynecologists. These men have had little training in abdominal surgery, yet they open the abdomen without hesitation, being totally unprepared to meet a number of situations which may be encountered.

With increased emphasis on specialist training by inference, one is to conclude that the so-called general surgeon is inadequate. The specialties, as we know them today, were developed in the main by men with broad background and training. With this as a foundation, they pushed the frontiers back. There is a tendency now to forget this broad background and training. Certain operations and diseases are concentrated upon, then one sets up as a specialist and feels that all such cases should be referred to him for care.

The American Board of Surgery is to be commended for its requirements and examination; its certificate has much merit. Certain specialties require

this as a basis, then with additional training, the man is able to take his examination in that specialty. There are others who want to restrict the field of their specialty in order to give the impression that only they are qualified. I am sure all have read the recent editorials in *Annals of Surgery* by Dr. Frank Glenn and Dr. Edward D. Churchill on this subject.

The last 100 years have been the rise of the specialty hospitals. We are beginning to see their fall. It is impossible to segregate a disease or an anatomic part of the body for treatment. There is a trend for the specialty hospitals to affiliate themselves with large general hospitals and medical centers. This serves to strengthen both. This will be hastened by the announcement that the American Board of Surgery, after July 1, 1950, will give credit for resident training only when such training has been received in hospitals offering graded residencies of three or four years' duration. This reflects the growing belief that the resident be given increasing responsibility and greater opportunities for advanced study and research as he progresses in his training. Remember, this was Halsted's idea 50 years ago.

How many graded residencies do we have? There are 62 government hospitals in this group; of this number 40 are under the Veterans Administration. There are 305 civilian hospitals with at least an approved program of 3 years. In all, 367 hospitals have been approved by the Council on Medical Education and Hospitals of the American Medical Association and the American Board of Surgery.

The Board of Regents of the American College of Surgeons, at its meeting in October, 1948, adopted a resolution increasing the minimum duration of graduate training in general surgery to at least 4 years of progressive training after the internship. For this training, there are 54 government hospitals and 282 civilian hospitals with approved programs, a total of 336.

It is clear the aforementioned hospitals will be besieged by applications and the others will have difficulty securing the type individuals they need. It is also evident that this group of hospitals will be called upon to furnish training for all general surgeons and also general surgical training for those going into specialties, in case they desire Board certification.

We in the Society of University Surgeons are fortunate. We have received the best surgical training it has been possible to obtain. Today, with 26 member hospitals and 203 members, our influence is becoming increasingly evident.

It is for us to carry on what John Morgan started and spread the light of knowledge through the whole American continent. Halsted wanted to develop teachers and surgeons of the highest type. How well he succeeded is shown by the number of Halsted-trained residents who are now professors of surgery, and that number is constantly increasing.

In the past, there has been a demand for well-trained surgeons of university background with a desire for an academic surgical career to go into smaller medical schools and institute resident programs. This demand, has, in large measure, been filled. The need now is twofold: first, to furnish this same type

man to the larger community hospital; second, to increase the teaching facilities for training surgeons to go into other and smaller community hospitals. A community hospital of 100 beds serving a town of 10,000 can adequately support a surgeon and such hospitals are now demanding men certified by the American Board of Surgery.

In order for these community hospitals to support such programs, they need help from the medical schools and medical centers. The community hospitals can furnish the clinical material for themselves and afford some for the medical centers. They need the medical centers to furnish facilities in basic sciences to men in the training programs.

It is our duty to lend a helping hand to these community hospitals, increase our sphere of influence, and affiliate the community hospitals with the university medical centers.

QUANTITATIVE ASPECTS OF HEMORRHAGE

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THE clinical tests usually employed to evaluate the severity of bleeding in acute hemorrhagic anemia do not always provide a clear picture of the situation. Moreover, quantitative balance studies designed to clarify the replacement needs of the acutely anemic individual have seldom been made.

Consideration was given these problems as part of a study of massive gastrointestinal bleeding due to peptic ulcer, involving 100 patients. Fifty-eight of these patients were treated by immediate operation for control of life-endangering hemorrhage. The following discussion will apply only to the fifty-eight patients in the operative group.

METHODS OF STUDY

Extensive studies were made on these individuals before and after operation. Plasma volume and total circulating red cell mass were measured, using the T 1824 dye technique.[1] These data are expressed in terms of percentage of normal. Information was obtained from each patient concerning his average weight in health; the normal plasma volume and red cell mass were then calculated on the basis of the generally accepted values of 44.8 c.c. of plasma per kilogram of body weight, and 36.5 c.c. of red cells per kilogram of body weight.

Determinations of the red cell count, hemoglobin, and hematocrit were carried out, and blood samples were analyzed for carbon dioxide, chloride, non-protein nitrogen, glucose, and protein content. In a number of cases, serum sodium and potassium values were measured. Every effort was made to rule out blood dyscrasias by routine tests of bleeding and clotting time, capillary fragility, prothrombin time, and examination of the peripheral blood smear.

Blood balance studies were made in ten cases of the operative series. Following the admission studies, the patients were immediately prepared for surgery and blood replacement was started. The quantities of blood transfused were carefully measured, and operative blood losses were also determined. In each case, hemostasis was so effective that the possibility of further hemorrhage after operation was negligible. The relationship between the predicted and actual red cell mass was determined in these cases. The predicted value was obtained by carefully calculating the volume of red cells transfused following the admission blood volume studies. If no cells were destroyed following transfusion, and if blood loss ceased at the time that bleeding was controlled, the patient would then have a predicted red cell mass at the end of operation equal to the sum of his admission red cell mass plus the transfused red cell mass. The actual red cell mass was measured repeatedly following operation. In each patient, plasma protein concentrations were determined frequently, and the plasma protein content of the transfused blood was also measured.[2]

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Read at the meeting of the Society of University Surgeons, Philadelphia, Pa., Feb. 9-11, 1950.

RESULTS

Table I illustrates the degree of anemia present in the operative series of fifty-eight patients before treatment. Twenty-seven patients had less than 40 per cent of their normal circulating red cell mass and three patients had less than 20 per cent of the theoretically normal value on admission to the hospital.

TABLE I. INITIAL VALUES FOR TOTAL CIRCULATING RED CELL MASS IN PERCENTAGE OF NORMAL, AS OBSERVED IN FIFTY-EIGHT PATIENTS WITH ACUTE HEMORRHAGIC ANEMIA

BELOW 20 (%)	20-39 (%)	40-59 (%)	ABOVE 60 (%)
3	24	24	7

Table II summarizes the degree of oligemia present in this group of patients. Eleven patients in the series were admitted to the hospital with blood volume values of less than 60 per cent of normal. In addition, twenty-seven individuals had suffered reductions of 20 to 40 per cent.

TABLE II. INITIAL VALUES FOR BLOOD VOLUME IN PERCENTAGE OF NORMAL, AS OBSERVED IN FIFTY-EIGHT PATIENTS WITH ACUTE HEMORRHAGIC ANEMIA

40-59 (%)	60-79 (%)	Above 80 (%)
11	27	20

A summary of the values for circulating red cell mass, hematocrit, and hemoglobin concentration in forty-five patients is shown in Fig. 1. The total circulating red cell mass, as measured by the T 1824 dye method before treatment, averaged 19 per cent lower than the hematocrit reading, and 14 per cent lower than the hemoglobin value. In twelve patients, the total red cell mass was

TABLE III. LABORATORY DATA FROM THREE PATIENTS WITH DEPLETED PLASMA VOLUME IMMEDIATELY FOLLOWING HEMORRHAGE

PATIENT	P. V.* (% NORM.)	R. CELL M. (% NORM.)	R. B. C. (% NORM.)	VC (% NORM.)
R. B.	62	33	68	70
C. K.	63	47	80	88
A. B.	83	56	81	84

*P.V. equals plasma volume; R.Cell M. equals total circulating red cell mass; R.B.C. equals red cell count; and VC equals red cell hematocrit.

more than 30 per cent lower than the hematocrit reading. Table III lists the blood findings in three representative patients studied before complete plasma hemodilution had occurred. In these patients, the plasma volume values were well below normal, and the red cell count and hematocrit did not indicate the true degree of anemia as shown by the figures for total red cell mass. The

TABLE IV. LABORATORY DATA FROM THREE PATIENTS AT A LATER STAGE AFTER HEMORRHAGE, PLASMA VOLUME BEING ELEVATED PRIOR TO THERAPY

PATIENT	P. V.* (% NORM.)	R. CELL M. (% NORM.)	R. B. C. (% NORM.)	VC (% NORM.)
A. M.	149	52	49	51
J. D.	138	45	40	49
S. L.	147	29	27	33

*P.V. equals plasma volume; R.Cell M. equals total circulating red cell mass; R.B.C. equals red cell count; and VC equals red cell hematocrit.

situation existing after the completion of hemodilution is illustrated in Table IV. In these individuals, the red cell count and hematocrit corresponded closely to the total red cell mass values, while the plasma volume levels were distinctly elevated.

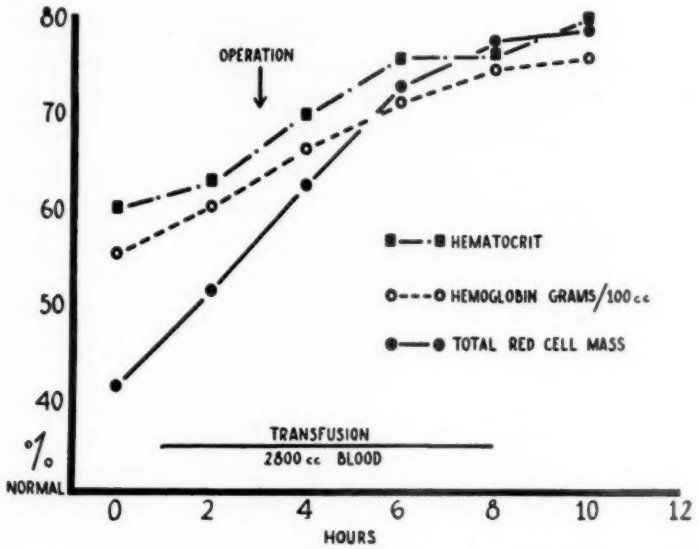

Fig. 1.—Postoperative values for circulating red cell mass, hematocrit, and hemoglobin concentration in massive hemorrhage from peptic ulcer. Therapy by operation and blood replacement. Values in forty-five cases are shown.

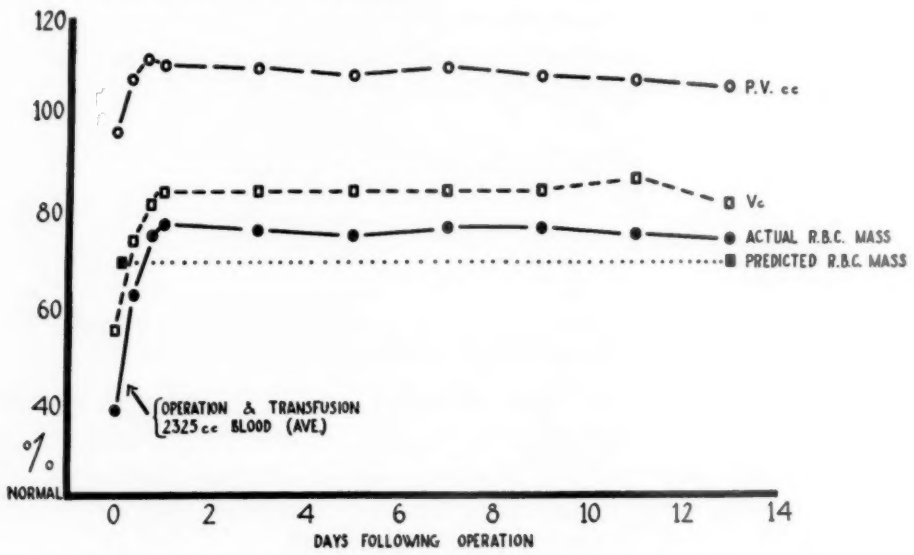

Fig. 2.—Postoperative values for plasma volume, circulating red blood cell mass, and hematocrit in massive hemorrhage from peptic ulcer. Therapy by operation and blood replacement. Average values of ten cases are shown.

Following completion of the initial blood volume studies, transfusions of whole blood were started, and large quantities were rapidly given, the average amount being 3,250 c.c. per patient. In the fifty-eight patients operated upon, the time interval between the beginning of blood replacement and the end of

operation (end of replacement), averaged ten hours. Hence, blood was replaced at the rate of 325 c.c. per hour for long periods. There was no evidence of intolerance to these transfusions.

Fig. 2 illustrates the blood volume data obtained from the ten cases in which balance studies were carried out. Following operation and transfusion of 2,325 c.c. of whole blood, the average total red cell mass increased from 38 to 78 per cent of normal. The relationship between the predicted and actual red cell mass values is shown graphically. The actual values deviate from the predicted red cell mass by 7 per cent on the average during the period of study.

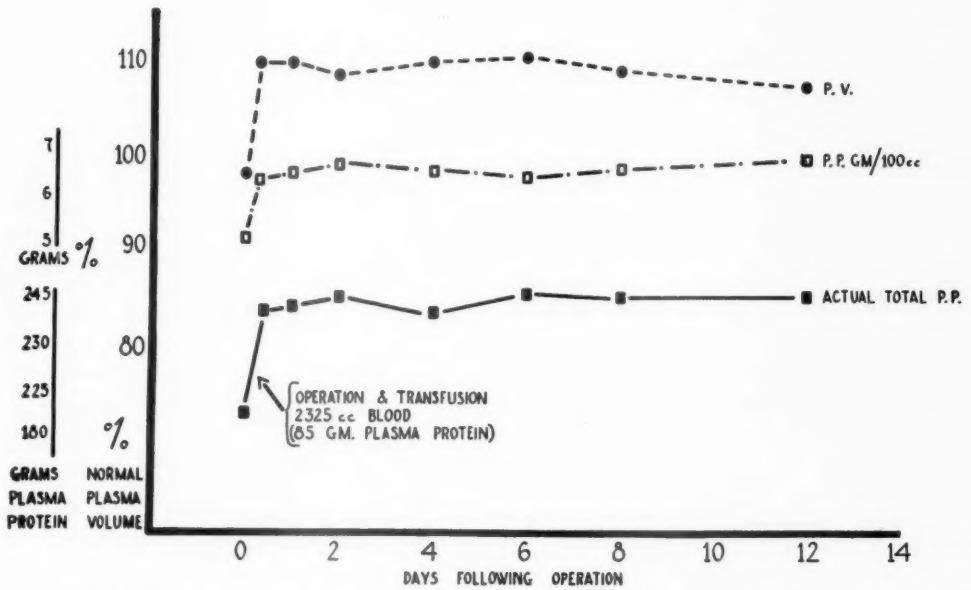

Fig. 3.—Postoperative values for plasma volume, total plasma protein, and plasma protein concentration in massive hemorrhage from peptic ulcer. Therapy by operation and blood replacement. Average values of ten cases are shown.

The plasma protein studies in the 10 cases are summarized in Fig. 3. The average admission total circulating plasma protein was 196 Gm., and the plasma protein concentration was 5.3 Gm. per 100 c.c. Each patient received an average of 85 Gm. of protein during transfusion. The postoperative values for total circulating protein rose to 246 Gm., and the plasma protein concentration rose to 6.8 grams per 100 c.c.

The average admission plasma volume in the 10 cases was 3,180 c.c. (96 per cent normal). The blood transfusions contained an average of 1,325 c.c. of plasma. Eight hours after operation, the plasma volume averaged 3,575 c.c. (108 per cent normal).

DISCUSSION

Tables I and II illustrate the severe degree of anemia and oligemia present in this group of fifty-eight patients. Analysis of the rate of bleeding further emphasizes the critical nature of the hemorrhage in these individuals. The symptoms were studied carefully in each case in order to obtain accurate information concerning the onset of hematemesis or melena. A summary of these

data indicates that forty-five patients (78 per cent) suffered major blood loss within twenty-four hours of admission to the hospital. Onset of bleeding in all other patients was within one week of hospitalization. Other potential hazards to survival were present in this group of patients. The average age was 54 years, and ten patients were more than 70 years old. Twenty-nine per cent of the patients showed evidence of significant cardiovascular or pulmonary disease when first examined (including severe hypertension, recent myocardial infarction, and active pulmonary tuberculosis).

The necessity for accurate evaluation of the bleeding patient's condition needs no emphasis. Following severe hemorrhage, the hematocrit falls slowly, and frequently does not truly record the degree of anemia for almost twenty-four hours. The hematocrit does not fall until the plasma volume begins to rise. It has been shown[3] that the plasma volume will not begin to increase until new plasma protein enters the circulation, carrying fluid with it. This process reaches completion in twenty-four to forty-eight hours, provided bleeding has ceased. Coincident with the peak value of plasma volume, the hematocrit reaches its lowest point. Many of our patients were studied before maximal hemodilution had occurred, and Fig. 1 demonstrates the discrepancy between total red cell mass and hematocrit measurements that may occur during this period.

The usual indices to anemia, namely, the red cell count, hemoglobin determination, and hematocrit, are all measures of red cell concentration, rather than total circulating red cell mass. The former values will obviously vary with changes in plasma volume, even if the total red cell mass remains constant. Not until all the red cells lost in bleeding are replaced by an equivalent volume of plasma will the hematocrit, red cell count, or hemoglobin fall to levels indicative of the true seriousness of the anemia. The pitfalls of relying on these tests in the first hours following severe hemorrhage are apparent. The full extent of the bleeding may be grossly and dangerously underestimated. Prior to the stage of maximum plasma hemodilution, there is only one reliable index to the extent of anemia, and that depends upon a measurement of the total circulating red cell mass, rather than any study expressed in terms of red cell concentration.

Since the discrepancy between total red cell mass and hematocrit measurements varies with the extent of plasma replacement after hemorrhage, it is frequently possible, in retrospect, to utilize the blood volume studies in reconstructing the history of bleeding. The picture as outlined in Table III is compatible with the onset of severe bleeding within twenty-four hours before admission to the hospital. On the other hand, values such as those shown in Table IV indicate a longer period of adjustment after hemorrhage.

In this study, an effort was made to evaluate the tolerance of the severely and acutely anemic patient to rapid blood replacement. Despite the large quantities of blood transfused, no patient showed evidence of cardiac embarrassment, even though seven individuals in the series suffered from obvious heart disease, and almost all were in the older age groups.

It is to be noted that 40 per cent of the patients were admitted to the hospital with plasma volume levels greater than 100 per cent normal. In eleven

instances, the plasma volume was greater than 125 per cent. Apparently such cases no longer have acute need for plasma, and, consequently, it might be advisable on theoretical grounds to consider the use of concentrated preparations of red blood cells as replacement therapy. Concentrated red cell suspensions have been used under varying conditions in the past,[4] but the results of this form of treatment do not appear to be well defined at present. It would appear possible that the use of red blood cells suspended in 5 per cent glucose solution, in cases of acute anemia with elevated plasma volumes, might be of some aid in minimizing the burden on the cardiovascular system resulting from large scale transfusions. This problem was not investigated in the present study. However, those patients seen early after hemorrhage, with depleted plasma volume as well as red cell mass, in all likelihood would still benefit more from whole blood transfusions than from injection of red blood cell suspensions.

Analysis of the blood balance studies makes it apparent that, despite large amounts of blood in replacement, the red cell mass was not restored to normal. Since average transfusions of 2,320 c.c. of blood were necessary to produce the 40 per cent increase in red cell mass (Fig. 2), it may be calculated that an additional 1,450 c.c. would be required to bring about restoration of a normal red cell mass. This total of 3,770 c.c. of blood is equivalent to 60 per cent of the normal blood volume, and emphasizes the large quantities of blood needed for adequate replacement, despite the fact that bleeding was controlled promptly in every case.

The relationship between the predicted and actual red cell mass in these cases is of interest. Fig. 2 demonstrates a close correlation between the predicted and actual values. This confirms the fact that the bleeding point has been controlled in these cases, and that the blood transfused has continued to circulate undiminished throughout the period of the study. The validity of this concept has been substantiated by extensive experience with blood replacement supported by laboratory measurements in hemorrhagic anemia. However, a theoretical uncertainty lies in the extent to which red blood cells previously not in active circulation may be mobilized in blood loss, and likewise the extent to which transfused red blood cells may leave the active circulation of the patient. The evidence from the present study, as well as recent findings in blood balance experiments on animals, suggest that the factor of red blood cell storage is of little consequence in the adjustments to severe hemorrhage.

The plasma protein data indicate that much of the transfused plasma protein left the circulation rapidly. Although both plasma protein concentration and the total quantity of circulating plasma protein rose to normal levels following transfusion, there was a loss of 35 Gm. of protein from the circulation. It would appear that a plethora of plasma protein is prevented by rapid removal of excess quantities from circulation. Presumably a considerable volume of fluid accompanied the shifting protein. Eight hours after operation, the plasma volume averaged 930 c.c. below the value expected on the basis of the volume of plasma transfused. As a result, the circulating plasma volume maintained a level consistent with the mild degree of anemia present postoperatively.

CONCLUSIONS

1. Individuals can survive large and rapid blood losses even in the presence of cardiopulmonary disease and old age; reduction of the total circulating red blood cell mass to 40 per cent in twenty-four hours may not be fatal.

2. Restoration of the red cell mass to normal in acute severe hemorrhagic anemia requires larger quantities of blood than was hitherto supposed.

3. Rapid transfusions of large quantities of whole blood can be safely carried out in cases of severe acute hemorrhagic anemia.

4. The T 1824 dye technique is a convenient guide to the severity of bleeding, especially in the early hours after onset of hemorrhage.

5. The red blood cell count and hematocrit are fallacious indices of hemorrhage.

6. Limitations on the ability of the organism in good nutrition to withstand severe hemorrhage are set by the factor of red blood cell mass rather than the factors of plasma protein, fluid and electrolyte.

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RETARDATION OF WOUND HEALING BY CORTISONE

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CORTISONE (E compound) retards the formation of granulations. It also slows, but does not stop epithelization. These observations have been made on man and on two different laboratory animals.

During the summer of 1949, one of us (Ragan) noted that biopsy wounds failed to heal in patients with different diseases treated with ACTH.[1] The problem of whether the delay was caused by the primary disease or by the elaboration of an adrenal hormone could not be distinguished clinically and consequently the problem was taken to the laboratory.

Here it was found that the rabbit and the rat possessed different susceptibilities for cortisone, but that in both species 17 hydroxy-11-dehydrocorticosterone prevented or markedly delayed the formation of granulations. Table I shows the various doses used on the rabbits. Skin defects made in the ears of rabbits still had blood vessels completely uncovered by granulations (8 days after wounding) with doses varying from 6 to 10 mg. per kilogram daily (Table I, Fig. 1). One-half the dose was given subcutaneously, morning and night, beginning three days before the wound was made. At operation no difficulty was encountered with bleeding and subsequently a small layer of fibrin formed on the wound. Grossly, these wounds remained free of exudate and, in fact, after eight days, were remarkably unchanged from the original appearance. Some epithelization took place, however, from the center island and from the edges of the wound, but not as much as had occurred in the controls. Quantitative blood plates showed that the number of bacteria on the surface of the treated wounds approximated the number found on the surfaces of the control wounds that had good granulations after four days under similar dressings of procaine penicillin in Amerchol H-9. Changes in the local dressings to calcium penicillin or sulfadiazine did not offset the inhibiting action of cortisone.

Microscopically, the tissues in the base of the wound did not increase in thickness (Fig. 2). They contained dilated large blood vessels surrounded by an increased cell population of round cells and fibroblasts with small nuclei. No new blood vessels or new reticulin fibrils were present. Mucopolysaccharides were diminished. Exudation on the surface was somewhat less than over the control wound. Some new granulations appeared, however, under the epithelium that advanced slightly from the edges of the wound.

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TABLE I

PARENTERAL DOSE	RESULTS
25 mg. per rabbit per day (8 to 10 mg. per kilogram)	Complete cessation of growth of granulation, 18 days; epithelization slowed
15 mg. per day (5 to 6 mg. per kilogram)	Same results for 12 days
7½ mg. per rabbit per day (3.6 mg. per kilogram)	Fibroblasts appeared around blood vessels on 9th day; onset of fibroplasia delayed; epithelization slowed
5 mg. per rabbit per day (2.0 to 2.3 mg. per kilogram)	Fibroblasts appeared around blood vessels in 7 to 8 days; onset of fibroplasia delayed; epithelization slowed

Smaller doses of cortisone, 2 to 3.6 mg. per kilogram, delayed the onset of the appearance of granulations for a shorter length of time (Table I). When they did appear, blood vessels, proliferating fibroblasts, and fibrils seemed to appear almost simultaneously although the number of new blood vessels was in excess.

Cancellation of the cortisone resulted in the reappearance of granulations four or five days later. Ragan made the same observation in patients.[1]

Healing of fractures has been delayed also in the rabbit by the doses of cortisone that arrested the generation of granulations. The technique used is the one recently described by Blunt and Hudack.[2] Details of these experiments will be given elsewhere, but a phenomenon was observed that escaped notice in the smaller wounds, namely, that hemorrhage was more slowly absorbed in the cortisone-treated animals.

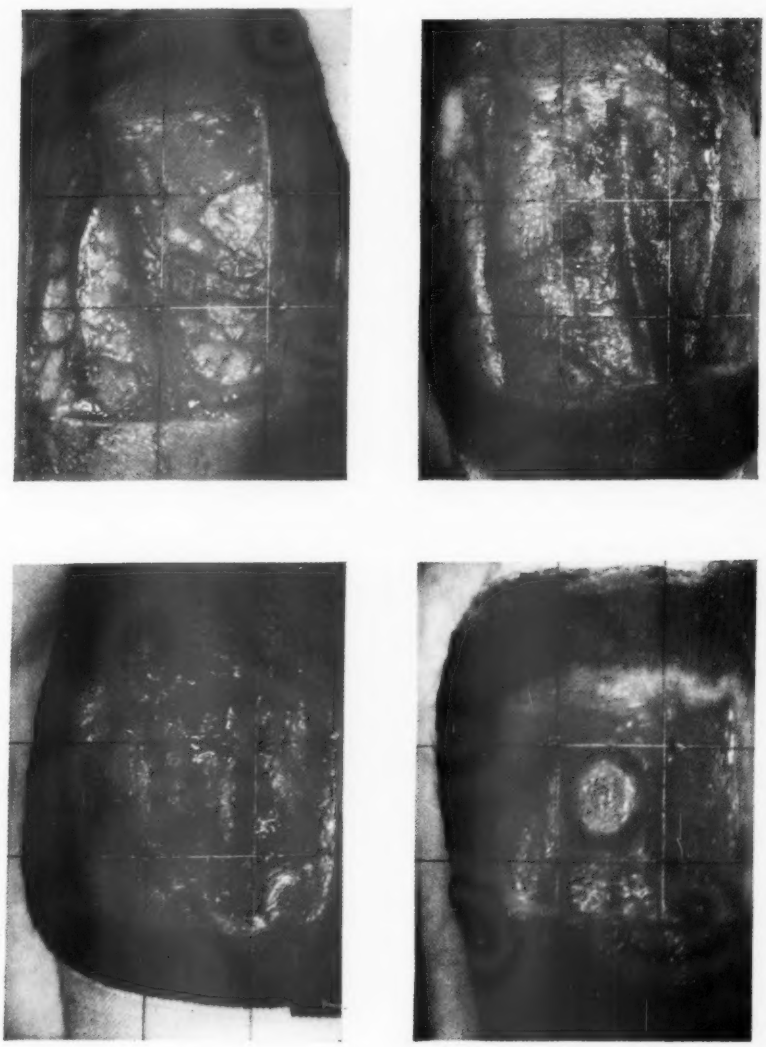
Healing of the open wound could not be observed satisfactorily in rats because bandages cannot be kept in place, and without them the wounds crust. Accordingly, the effect of cortisone had to be evaluated in this animal by testing the tensile strength of sutured wounds. Two groups of five rats were injected daily, beginning three days before operation with 5 mg. (20 mg. per kilogram) and 10 mg. (40 mg. per kilogram), while the controls were left untreated. On the sixth day of healing the average bursting strength of sutured wounds of the stomach was 111 mg. of Hg in the control animals, 95 mm. in the group receiving 5 mg., but only 77 and 73 mm. of Hg, respectively, in two groups receiving 10 mg. Muscle wounds averaged only 304 Gm. per centimeter in the cortisone-treated (10 mg.) rats, while the controls averaged 574 Gm.

TABLE II. SUMMARY SHEET, CORTISONE-TREATED RABBITS

RABBIT NUMBER	TOTAL DOSE (MG.)	DOSE (MG. PER KG.)	DURATION OF WOUND (DAYS)	DURATION OF CORTISONE (DAYS)	WEIGHT LOSS (KG.)
74	5	2.3	8	10	−.09
75	5	2.0	7	9	−.35
68	7.5	2.4	11	14	+.02
69	7.5	3.6	5	8	+.21
66	15	5.0	5	8	+.23
67	15	6.6	8	11	−.28
62	25	10.2	14	19	−.57
63	25	10.0	14	11	−.60
54	25	12.5	8	11	+.18
55	25	10.2	5	8	−.17
56	25	8.0	8	11	−.32
57	25	9.1	5	8	−.15

Treated, 5 days.

Treated, 8 days.



Control, 5 days

Control, 8 days

Fig. 1.—Control wounds, fifth and eighth days (bottom). Experimental wounds, treated with cortisone fifth and eighth days (above).

Note: Control wounds have excellent granulations by the fifth day, excellent epithelization by the eighth day.

Experimental wounds have no granulations. Blood vessels and nerves are exposed. Rim of epithelium has definiteiy appeared at the margin of the treated wound and about the center island by the eighth day.

In the same way, skin wounds averaged only 160 Gm. in the cortisone-treated (10 mg.) animals, while the controls averaged 260 Gm. All these figures indicate that fibroplasia was delayed in the rats under the influence of cortisone, but that some was occurring to give a certain amount of strength. Perhaps these rats should have had still more cortisone to block the process entirely. Yet fibroplasia also progressed under the advancing edge of epithelium, whereas it was stopped completely in the center of the open wound. Or perhaps, with a slitlike defect, such as a sutured wound, some nourishment is received from old blood vessels in the adjacent tissues.

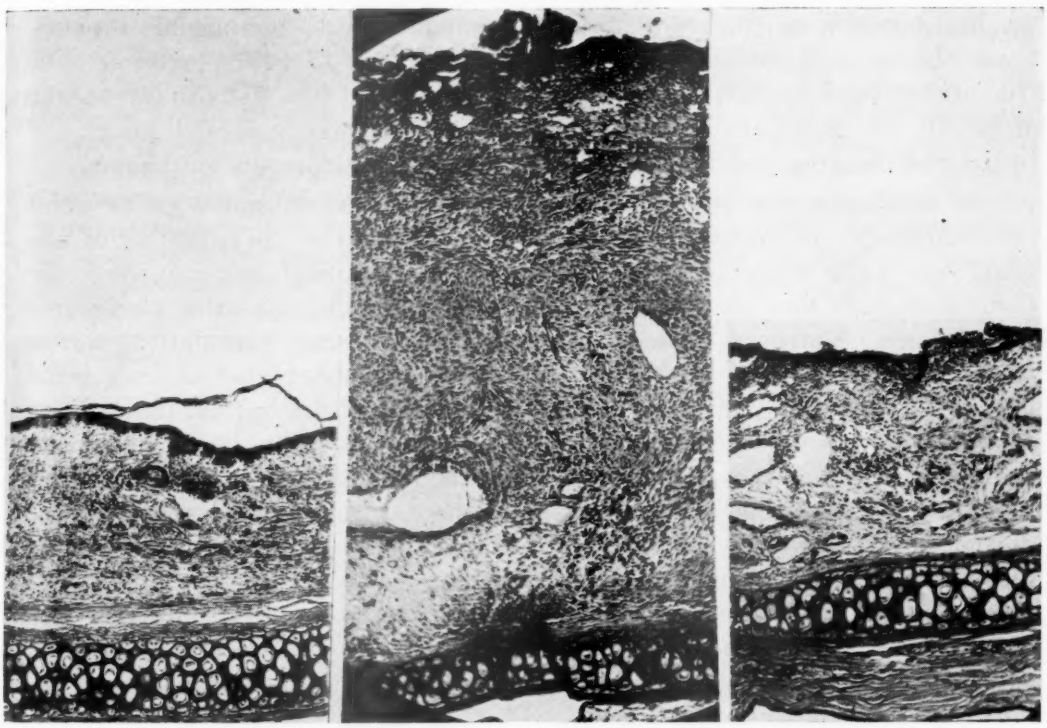


Fig. 2.—Cross section of normal rabbit's ear, left; eight-day granulating wound, center, control; and right, eight-day granulating wound of animal treated with cortisone. Note the thickness of connective tissue and the cell density in the normal ear. In the control wound, the granulations are higher, there are many fibroblasts with collagen fibrils, and many capillaries are seen. Two old, large, dilated blood vessels are present. The cortisone granulations are not much thicker than the normal connective tissue of the ear and all the old large blood vessels are dilated. There are no new capillaries. However, the cell concentration, particularly of the round type and of a type resembling fibroblasts, is increased. These cells show few signs of proliferating. There is less exudate on the surface than on the control granulations.

Some explanations can be given for the action of cortisone that might explain the mechanism whereby it retards the formation of granulations. Cortisone causes an eosinopenia and profoundly changes metabolism. Catabolism exceeds anabolism, uric acid is excreted, and marked glycogenesis occurs. The rabbits did not suffer profound weight losses. Some lost, others gained slightly (Table II). Their liver cells were so distended with glycogen that only the outlines of the cells were seen. One animal showed an increased blood sugar. A depletion of Vitamin C would not seem to account for the results, for the content of Vitamin C in the plasma, in the adrenal glands, and in muscles was not significantly

TABLE III. VITAMIN C CONTENT

	CONTROL	CORTISONE-TREATED
Plasma	.028 to 0.65 mg. per 100 c.c.	0.34 to 0.42 mg. per 100 c.c.
Adrenal glands	130 mg. per 100 Gm.	83 to 199 mg. per 100 Gm.
Muscle	.678 mg. per 100 Gm.	.69 mg. per 100 Gm.

altered (Table III). Similarly, a change in concentration of serum protein seems to be excluded. Total proteins averaged 5.7 Gm. per cent in cortisone-treated rabbits, and 5.8 Gm. per cent in the controls. Change in vessel permeability, interference with some enzyme system, or the direct toxicity of an excessive amount of cortisone that prevents the sprouting of blood vessels and the proliferation and differentiation of fibroblasts are better possible explanations. In favor of the last one is the observation that 15 mg. of cortisone in 25 Gm. of Amerchol applied locally in amounts of about 1 Gm. daily to ear wounds of rabbits, prevented the growth of granulations for twenty days, although epithelization occurred and fibroplasia again took place under the epithelium.

In conclusion, the observation that a hormone-like substance exists which can completely stop such profound defense mechanisms as the sprouting of new blood vessels and fibroplasia is not only significant in itself, but conversely, the finding suggests that an offsetting mechanism must likewise exist whenever a wound heals. Moreover, we have always been taught that granulations were a barrier against surgical infections, yet in the cortisone-treated animals infection of the wound did not take place, although granulations did not form. These wounds were not, of course, severely challenged by bacteria, but still, without any particular care to protect them, infection did not occur. In addition, although fibrin did form on the surface of the cortisone-treated wound, fibrin did not act as a scaffold for the growth of granulations and was not converted directly to collagen, although proliferating fibroblasts were not present. Both theories have had ardent proponents in the past. Last, that epithelial cells advancing by ameboid motion or by division are able to initiate fibroplasia in an environment where previously the process did not exist is a phenomenon that must not escape our attention.

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DISCUSSION

DR. C. R. HANLON.—I have enjoyed this presentation and I am sure that Dr. Howes has carefully refrained from drawing any clinical conclusions. I want to report on one case which is relevant to some of these observations.

This was a man with periarteritis nodosa who had severe diarrhea and weight loss, and was being treated with ACTH for that condition. He had undergone biopsies of skin and muscle before and after initiation of treatment; all of these wounds had healed well.

During the course of this treatment he developed generalized peritonitis due to perforation of a Meckel's diverticulum. The correct diagnosis was not made before exploration which was carried out through an upper midline incision, followed by a right McBurney

incision. The abdomen was full of pus, originating from the right lower quadrant. The upper midline wound was closed without drainage and drainage was instituted through the McBurney incision. There was no infection either in the drained wound or in the upper midline wound, nor was there any gross interference with healing as judged, of course, by simple clinical criteria.

The wounds appeared to heal much as they would have healed had the therapy with ACTH not been in effect. We were somewhat chary of carrying out these operations because of the poor wound healing which is reputed to occur under such therapy. One of course cannot draw any conclusions from a single case, but at least under the dosages given and under the stated conditions, there appeared to be no gross interference with healing.

DR. E. L. HOWES (Closing).—On the other hand, we have been given reports of individuals who received ACTH or cortisone before operation and developed leaking anastomoses. It is always difficult to evaluate cause and effect clinically, and I think the combination of the two should certainly be avoided until we have more information.

Again, the nonhealing wounds seen clinically may originate by a disturbance similar to the cortisone mechanism. In most instances, nonhealing is a local phenomenon and the general one is more unique. Some of Conrad's pictures just shown, illustrating large unhealed areas existing in paraplegic patients, suggest a general cause for the delay. Previously I have not been able to find altered skin temperatures in such patients although sensations were absent. One cannot help but wonder, therefore, whether the mechanism that really exists is not similar to the one behind the cortisone action. In this regard our attention is being constantly drawn to the liver, and I think if you will review your own cases of nonhealing, you will find a high proportion with pathology of the liver.

SODIUM DEFICIENCY IN SURGICAL PATIENTS AND THE FAILURE OF URINE CHLORIDE AS A GUIDE TO PARENTERAL THERAPY

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THE material presented in this paper represents a continuation of a series of reports on the study of fluids, electrolyte, and nutritional problems on the Surgical Service of the Presbyterian Hospital. These studies began in June of 1947 with the completion of a flame photometer, which made possible rapid and accurate sodium and potassium determinations on biologic media, and were greatly accelerated with the opening, in January, 1948, of the surgical metabolic unit. Since that time patients have been studied in the unit according to planned programs and, simultaneously, the conditions of critically ill patients on the general service have been evaluated on a day-to-day basis as a guide to therapy. This paper reports some of our experiences, with particular emphasis on acute sodium deficiency, and presents an evaluation of urine electrolyte excretions, particularly urine chlorides, as a guide to parenteral sodium and chloride replacement therapy.

REVIEW OF PERTINENT LITERATURE

The problems confronting the surgeon with regard to fluid and electrolyte balance are essentially those of keeping volume of water and concentrations of electrolytes at the optimum level. Much work has been done illustrating the effects of depletion of the extracellular fluid of water and electrolytes, and, more recently, studies indicate that intracellular volume and concentration require active consideration as well.

Sodium, chloride, and bicarbonate ions are the major portion of the electrolyte structure of extracellular fluid, and depletion of "salt," and specifically of sodium and chloride ions, has been the subject of many studies. McCance,[1, 2, 3] in an excellent series of studies, brought together the knowledge of sodium chloride deficiency and demonstrated experimentally in man that definite signs and symptoms resulting from sodium chloride depletion were rapidly corrected when sodium chloride was administered. Water loss did not play a prominent part in his studies, but he observed loss of weight, largely water, and increased nitrogen loss as the result of sodium chloride depletion. He also observed a rise in the serum urea nitrogen in salt depletion, a phenomenon recently studied by Schroeder[4] as associated with low sodium in cardiac patients treated with mercurial diuretics. Schroeder recommended hypertonic sodium chloride in treatment to avoid increasing volume unnecessarily while increasing concentration.

Elkinton, Danowski, and Winkler[5] clarified the hemodynamic changes in salt depletion in dogs, pointing out that acute sodium chloride deficit produced

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circulatory changes similar to the peripheral vascular collapse seen in burns, trauma, and hemorrhage, and that salt depletion shock was rapidly reversible with sodium chloride administration. They pointed out that a loss of 30 per cent of available sodium and chloride was sufficient to produce it. They noted a decrease in circulating protein in the depleted state. They also noted[5, 6] that water depletion alone did not produce nearly as great an effect and that a combination of water loss with low electrolytes in the remaining fluid was productive of the greatest shock.

Danowski, Winkler, and Elkinton[7] reported that deficiencies in circulating protein were eliminated when either hypertonic or isotonic saline solution was infused, while glucose infusions had little effect on either shock or protein deficit.

In discussing water and salt depletion, Marriott[8] stated that when less than 0.5 Gm. of sodium chloride per kilogram, is lost, symptoms are limited to vertigo and orthostatic hypotension; when losses are from 0.5 to 0.75 Gm. per kilogram, anorexia, nausea, and occasional vomiting are seen; and when losses exceed 0.75 Gm. per kilogram, circulatory collapse follows.

Peters[9] warned against the effects of low serum sodium on cellular overhydration, renal function, and circulation, and stated that patients may develop edema with low sodium. He advocated the use of hypertonic (3 to 5 per cent) sodium chloride when sodium is low and edema present. In discussing the role of sodium in the production of edema, he emphasized the necessity for individualization in the consideration of cases and a study of the status and mechanisms of imbalance in each.

There is ample evidence, however, that excessive amounts of sodium chloride lead to major difficulties. Coller and associates[11] sounded a now-classical warning to surgeons in their article on postoperative salt intolerance, demonstrating that postoperatively sodium chloride was held and not excreted, and excessive use led to edema. They demonstrated[12] in a series of cases that between 350 and 400 meq. of Na and about 300 meq. of Cl were retained if the patients were infused with either isotonic or 0.75 per cent sodium chloride solutions. Renal excretion was far below expected levels, and intracellular water was mobilized to maintain osmotic equilibrium with resultant loss in potassium. Limbert and his associates[13] demonstrated that retention of sodium chloride can result in marked oliguria when kidneys do not excrete the ions in the postoperative phase.

Fantus,[14] in 1936, made some excellent observations on the relationship of fluid administration to postoperative recovery, as well as reporting the urine chloride test which now bears his name. He noted that mortality increased when urine chloride was less than 0.2 per cent or when it was very high, and he speculated as to whether or not many of the difficulties seen might be due to the administration of too much salt and water as well as too little. He also advocated the use of 3 per cent sodium chloride in primarily salt-depleted cases. He advised less routine treatment and more individualization of cases, including the keeping of careful balance sheets postoperatively. More recent observations certainly substantiate the importance of these recommendations.

The Fantus test or modifications of it have been advocated in recent papers as a method of determining urine sodium chloride excretion, and, under some circumstances, of measuring the amount of parenteral sodium chloride needed. Marriott[8] suggested that a urine chloride equal to less than 0.5 Gm. NaCl per liter indicated salt depletion, and urine chloride equal to 5 Gm. NaCl per liter showed no depletion. He stated that measurement of sodium would be preferable to measurement of chloride.

Van Slyke and Evans[15] used the Fantus method of urine chloride determination as a guide to the detection of salt depletion and its correction. They warned against renal impairment as invalidating the method and suggested giving saline solution if urine sodium chloride was less than 3 Gm. per liter, and dextrose in water if this concentration was exceeded.

Bryant and associates[16] suggested a modification of the Fantus test as a method for maintaining hypertensive and cardiac patients on a low salt diet, and they showed correlation tables which demonstrated considerable error between test-calculated and actual excretions. However, they recommended it as an easy and approximate guide to salt intake.

Certain major errors in assuming that sodium equals chloride in the urine, however, are evident. Farnsworth,[17] in discussing patients with edema, pointed out that in decompensated cardiac patients the ratio of sodium to chloride in the urine was far from 1 to 1, but averaged 0.40. In patients with cirrhosis of the liver the average ratio was 0.25, while in normal patients it was 0.90.

Goldzeiher and Stone[18] reported on patients who were given a test dose of sodium chloride while on balance studies and showed that the correlation of urine sodium to chloride was only fair and was quite variable. They urged determining individual ion values in balance studies.

METHODS

All of the patients in the potassium study groups (Groups 1 and 2), the gastrectomy groups (Groups 3 and 4), and patients G. S. and M. P. were studied in the surgical metabolic unit, where complete and accurate measurements of all intakes and outputs are readily controlled. Patients J. H., B. H., and the fourteen major postoperative cases (Group 5), as well as the peritonitis and cardiac sodium-deficiency groups, were on the general surgical wards, where, however, with occasional exceptions, specimens from sick patients are handled as they are on the metabolism ward.

Sodium and potassium determinations in plasma, urine, stool, and drainages were done with a modification of the internal standard flame photometer introduced by Barnes, Richardson, Berry, Hood, and Chappell in 1946.[19, 20] This instrument has a reproducible accuracy of 1 per cent for both sodium and potassium and has the advantage of requiring only 1 to 2 c.c. of specimen. Chloride ion determinations were done by the method of Schales and Schales.[21] Bicarbonate determinations were done as CO_2 content by the method of Van Slyke. Blood samples were taken, except in emergencies, in the early morning before the day's fluids or food were started. When HCO_3 was to be tested for, blood samples were taken under oil and allowed to clot, and then all determina-

tions were done on the serum. Sodium and potassium determinations alone were done on plasma from blood collected with careful precautions to avoid hemolysis; the blood was placed in a 5 c.c. hematocrit tube containing approximately 0.1 mg. sodium heparin. This was immediately centrifuged, and the determinations were made on the plasma. Urines, Miller-Abbott tube drainage, and other drainages were collected as twelve or twenty-four hour specimens in covered containers. In computing outputs of water and electrolytes, care was exercised that exact measurements were made and that irrigating fluids (as in Miller-Abbott tubes) were included in intake, and irrigation returns included in output.

The coefficient of determination used in expressing correlations between urine sodium and chloride is the square of the coefficient of correlation and is used to express relation between the two variables in terms of per cent. The formula[21a] used is:

$$r = \frac{N \Sigma XY - \Sigma X \cdot \Sigma Y}{\sqrt{[N \Sigma X^2 - (\Sigma X)^2]\,[N \Sigma Y^2 - (\Sigma Y)^2]}}$$

Where r = coefficient of correlation (r^2 = per cent), N = number of cases, X = sodium concentrations in meq., Y = chloride concentrations meq. per liter, and Σ = sum of.

In all of the determinations there is a very highly significant correlation between sodium and chloride ions, but the degree of correlation is highly variable. Patients on diet would be expected to show correlations of 80 to 90 per cent if they quantitatively excrete their intake, and this is the case. However, when the patients are on parenteral fluids, where sodium and chloride ion intakes are equal or nearly so, the correlation should approach 100 per cent if sodium and chloride ions are excreted together equally. A drop to 70 per cent correlation indicates significant discrepancy, to 55 per cent highly significant, and below 50 per cent very highly significant discrepancy in ionic correlation. In comparing figures, a difference in r^2 of 10 per cent is significant in all groups except for comparison with Figs. 5 and 8, where small numbers require a 20 per cent difference for significance.

Acute Sodium Deficiency.—The cases of markedly decreased serum sodium which we have seen on the surgical service since 1947 fell into four general categories: (1) patients with acute peritonitis; (2) patients with borderline cardiac reserve in whom sodium chloride was administered too cautiously or not at all; (3) patients with ileostomies; and (4) patients with other gastrointestinal tract losses in whom the volume of fluid and extent of electrolyte loss was not appreciated soon enough, or replacement was insufficient.

In the acute peritonitis group, peritonitis followed either leakage of intestinal anastomosis, perforation of small bowel secondary to regional enteritis, or the accumulation of bile intraperitoneally secondary to biliary tract surgery. Characteristic was a sudden drop in serum sodium level concurrent with or shortly followed by peripheral vascular elapse.

The case of M. B. is illustrative. He was a 16-year-old youth with a six months' history of a severe ulcerative colitis who had had three previous admissions to the Medical Service. All conservative therapy had failed, and because of the progress of the disease, it

was decided to resect the colon. Accordingly, after 2,500 c.c. of blood over a week's period, a right hemicolectomy and ileotransverse colostomy was performed on Dec. 13, 1947, with a colostomy of the distal transverse colon. A Miller-Abbott tube was introduced preoperatively. Postoperatively he did fairly well on a regime of 2,000 c.c. of saline solution a day to compensate for Miller-Abbott tube drainage. On the fifth day the Miller-Abbott tube was removed, and he was started on liquid food by mouth. This day the serum electrolytes were Na 131.6, K 4.0, HCO_3 24.6, and Cl 97.0 meq. per liter. The sixth day there was rather profuse colostomy drainage, and he received 1,500 c.c. of 5 per cent dextrose in saline solution in addition to 1,700 c.c. of fluids by mouth. At 4:30 A.M. the seventh day he went into shock, blood pressure 80/60, pulse 160 to 180, skin cold and wet. Abdominal signs were moderate tenderness, no spasm, rebound tenderness moderate throughout. Chemistries at this time were hematocrit 50, serum Na 116, K 4.1, Cl 93 meq. per liter. After administration of 1,500 c.c. saline solution and 500 c.c blood, Na was 125.4, K 4.1, and Cl 100 meq. per liter. Blood pressure was 50/0. After 500 c.c. more of blood and 500 c.c. saline solution, the hematocrit was 40, Na 126.8, K4.1, Cl 96.5 meq. per liter. The patient then received 1,000 c.c. M/6 sodium lactate and 500 c.c. saline and glucose solution with 25 Gm. of albumin. The blood pressure did not rise above 50/0, and he was completely anuric. The following day plasma Na was 132, K 4.15, Cl 96.9 meq. per liter, and the hematocrit was 41.5. The patient received 1,000 c.c. of blood, 500 c.c. of plasma, 2,000 c.c. of glucose and saline solution with 50 Gm. of albumin. He developed edema of the chest wall and sacrum and finally expired. At post-mortem a diffuse generalized fibrinopurulent peritonitis was found secondary to leakage of the ileotransverse colostomy, and in addition marked amyloid disease of liver, spleen, adrenals, and kidneys.

B. H. was a similar case, except that she developed generalized peritonitis following spontaneous perforation of a fistula secondary to long-standing regional enteritis and went into shock with marked hypotension. She was found to have a serum sodium of 121 meq., K of 5.4 meq., and Cl of 82.6 meq. per liter, although previous levels had been well maintained.

The cardiac group is an interesting one and illustrates the value of direct serum sodium determinations.

C. W. was a 76-year-old man who entered the hospital Nov. 19, 1948, with a chief complaint of six days of intermittent right upper quadrant pain, severe for twenty- four hours, and accompanied by anorexia but no vomiting. Associated history included bronchial asthma for forty years, hypertension for several years, two years of attacks of moderately severe substernal pain, relieved by rest, and six months' history of cough with occasional frank hemoptysis. Blood pressure was 190/90, temperature 99.8° F., white blood cell count 19,000, 86 per cent polymorphonuclear forms. Fine râles were heard posteriorly in both lung fields, but more on the left. There were marked tenderness and spasm in the right upper quadrant. An x-ray picture of the chest was strongly suggestive of carcinoma in the right hilar region. Conservative measures were employed for twenty-four hours, but the white blood cell count rose to 26,800, 94 per cent polymorphonuclears, the temperature rose to 101.6° F., and the patient began to vomit. The skin was gray and clammy; blood pressure fell to 154/95. He was digitalized intravenously, and a cholecystostomy was performed under intercostal block and local anesthesia. During the operation the blood pressure fell to 120/80. An empyema of the gall bladder was drained, and several stones were removed. Postoperatively he was cyanotic in an oxygen tent. The skin was cold and wet, but the lungs were "remarkably clear." Numerous premature auricular beats were heard. He received a total of 2,500 c.c. of dextrose in water by vein and clysis the operative day, and 2,000 c.c. of dextrose in water on the first postoperative day. He remained cyanotic, weak, with gray clammy skin. By evening the blood pressure had returned to 190/100, but he showed no other improvement. There was no urine output. The second postoperative day values showed hematocrit 60, morning electrolytes Na 128.5, K 4.0 meq. per liter. At 6 P.M. Na was 120, Cl 87 meq. per liter despite 1,900 c.c. of a liquid diet by mouth, and the skin was cold, wet, and the patient cyanotic. He was then given 2,000 c.c. of 0.85 per cent dextrose in saline solution, and

750 c.c. more the following morning. He voided 100 c.c. the second postoperative day. The third postoperative day he was considerably improved; the skin was warm and dry, and slight cyanosis persisted but was much less than previously. He voided 800 c.c. this day, 1,300 the next, and 2,500 the fifth postoperative day. Despite this, serum urea nitrogen was 100 mg. per cent on the sixth day and then slowly fell to normal. By the sixth postoperative day, without further parenteral sodium, serum Na was 146 meq. and K 3.6 meq. per liter. Bile drainage was a maximum of 400 c.c. on first postoperative day and then declined slowly. Six months later he was reported by his local doctor as recovered from the gall bladder operation but still a cardiac invalid.

M. L. was a 48-year-old alcoholic who entered the hospital three weeks after fracturing three ribs in a fall, and was found to have an empyema of the left chest, which was drained. She developed a Type VI pneumococcus meningitis which was treated with intrathecal penicilin. Serum electrolyte values on the third postoperative day were Na 123, K 2.8, HCO_3 27.2, and Cl 84.1 meq. per liter with total protein of 4.32 Gm. per cent. She received 4,400 c.c. of fluid with 110 meq. of Na and 70 meq. of Cl before values were known. The fourth day serum Na was 123, K 3.9, HCO_3 21.2, and Cl 87 meq. per liter. She received 3,000 c.c. of fluid, 220 meq. of Na, and 280 meq. of Cl and developed sacral edema and right and left heart failure; venous pressure was 180, urine output was 850 c.c. She was digitalized and because of low serum protein was given 75 Gm. of albumin, one liter of saline solution, and 2,000 c.c. of dextrose in water. On the fifth day urine output rose to 2,850 c.c., and cardiac compensation improved progressively On the sixth day she received 110 meq. Na, 140 meq. Cl, 30 meq. K, and 25 Gm. albumin in 1,000 c.c. water, and urine output was 3,200 c.c., with urine Na 6 meq., K 17 meq., and Cl 7 meq. per liter. By the eighth day, without additional sodium chloride, but with a total of 175 Gm. of albumin and continued digitalization, serum Na was 141 meq. per liter, K 3.3, and Cl 104.3 meq. per liter, and HCO_3 22 meq. Her course was stormy, but she eventually recovered.

J. H., 76-year-old widow, came to the Presbyterian Hospital on June 13, 1948, with a history of nine months of left lower quadrant pain of dull, almost constant variety, punctuated with three episodes of severe pain accompanied by nausea and vomiting. From October, 1947, to the date of admission she was never free from a low-grade nagging pain in the left lower quadrant. She never had any change in caliber of stools or any blood or mucus. She lost some weight but the amount was not certain.

Physical examination revealed a very thin, elderly woman who looked acutely and chronically ill. Blood pressure was 190/110; there were moist râles at the base of both lungs, but no edema of the extremities. Heart was minimally enlarged. There was a slightly tender mass easily palpable in the left lower quadrant. Chest x-ray examination was compatible with mild decompensation, clearing, as did the râles, after digitalization. Barium enema revealed a narrowing in the mid-sigmoid together with numerous diverticulae. Carcinoma could not be excluded by x-ray examination. Hemoglobin was 12.3 Gm. per cent, red blood cell count 3.9, and blood urea nitrogen 14 mg. per cent. The patient was given 1,000 c.c. of blood, following which hematocrit was 41.2 and plasma proteins were 6.55 Gm. per cent.

At operation a carcinoma of the sigmoid was found, and a resection and anastomosis was done, together with a cecostomy. The patient was given 1,000 c.c. of whole blood and 1,500 c.c. of dextrose in water the operative day. She did well for the first twenty-four hours and had a urinary output of 850 c.c. Following this, despite 2,500 c.c. dextrose and water the second day and 1,500 c.c. the third day, she became progressively more lethargic, and by the third day her urinary output was 0. At this point initial determinations were done. The hematocrit was 55, plasma protein 7.44, HCO_3 20.8, Na 121 K 4.5, and Cl 84.3 meq. per liter. Sulfadiazine level was 10 mg. per cent, and there was gross blood in the few cubic centimeters of urine obtained by catheterization. Blood urea nitrogen was 45 mg. per cent. The blood pressure was 140/80. It was estimated that she had an extracellular fluid volume deficit in excess of 3.5 L. and that the total sodium deficit was in excess of 600 meq.; the chloride ion deficit was about 450 meq. The heart was fibrillating at a rapid rate. As was expected, the serum potassium was high. As Fig. 1 shows, 8,600 c.c. of fluid were given parenterally in about forty hours without evidence of edema or failure and with a resumption of renal output and

general improvement. Subsequent events proved that the intracellular debt in water was about 7,000 c.c. The serum potassium level fell rapidly with rehydration, and then with supplemental potassium it was brought back to nearly normal, to fall rapidly with an episode of diarrhea, and then to resume its gain with extra potassium and the cessation of the diarrhea.

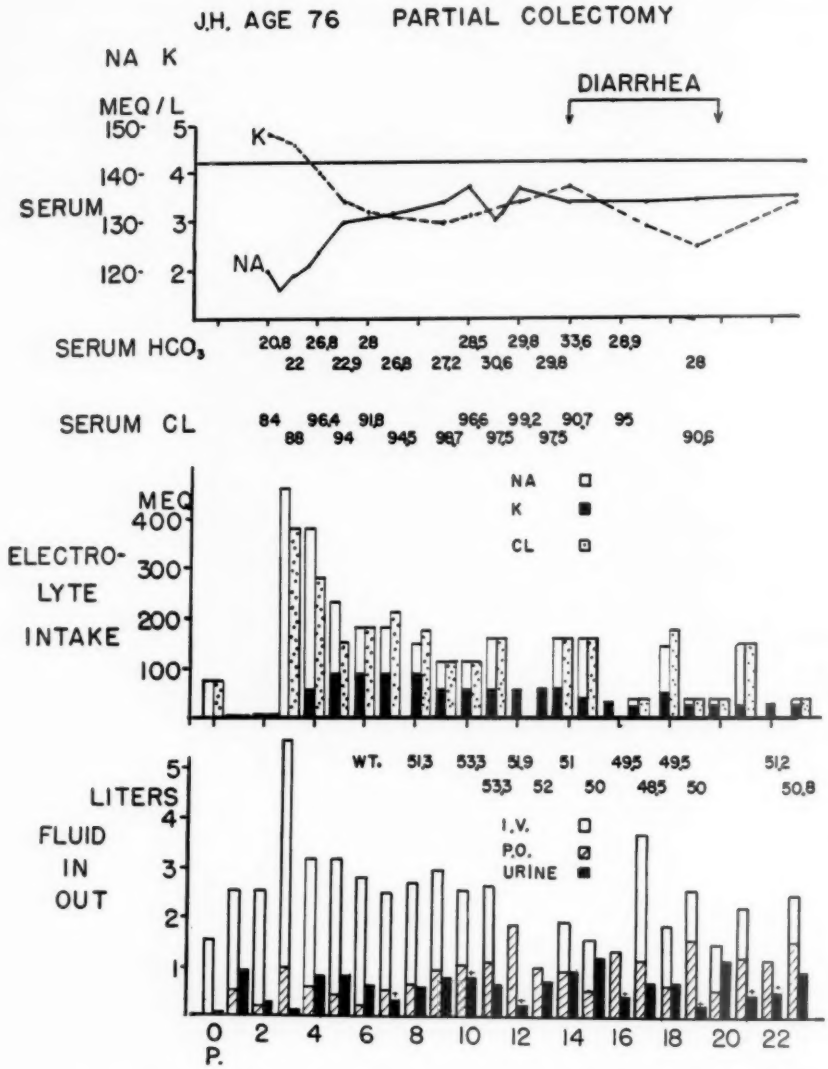

Fig. 1.—Postoperative sodium deficiency and dehydration in a 76-year-old hypertensive cardiac patient following failure to administer sodium and chloride postoperatively. Recovery following massive replacement.

A blood volume study done forty-eight hours after the start of intensive rehydration showed plasma volume reduced 20 per cent and red blood cell mass elevated 10 per cent. Plasma proteins of 5.3 required limitation of further hydration, in spite of the elevated red cell mass, to maintain a balance between the two. Further whole blood transfusions had to be limited, and a solution of amino acids was given to provide protein equivalent, although we are sure the amounts given were not sufficient to provide a positive nitrogen balance.

Note that large amouts of sodium and chloride ions were given to replace both the low values and to provide electrolytes to hold the water given to re-expand the extracellular fluid volume, and that once this was accomplished, the sodium was markedly restricted in order to prevent overexpansion of the extracellular fluid, which might result in edema and cardiac

failure. At no time did this patient exhibit any edema, either peripheral or pulmonary, or have a venous pressure over 100 mm. of water, and even this venous pressure was only at the conclusion of the rapid phase of rehydration and dropped to 50 mm. within four hours. Potassium was administered both parenterally and by mouth. The oral dose probably was not well absorbed until the ileus began to clear, and more should probably have been given parenterally during this phase. Her postoperative recovery was slow, but she was alive and fairly well in October, 1949, fifteen months after the operation.

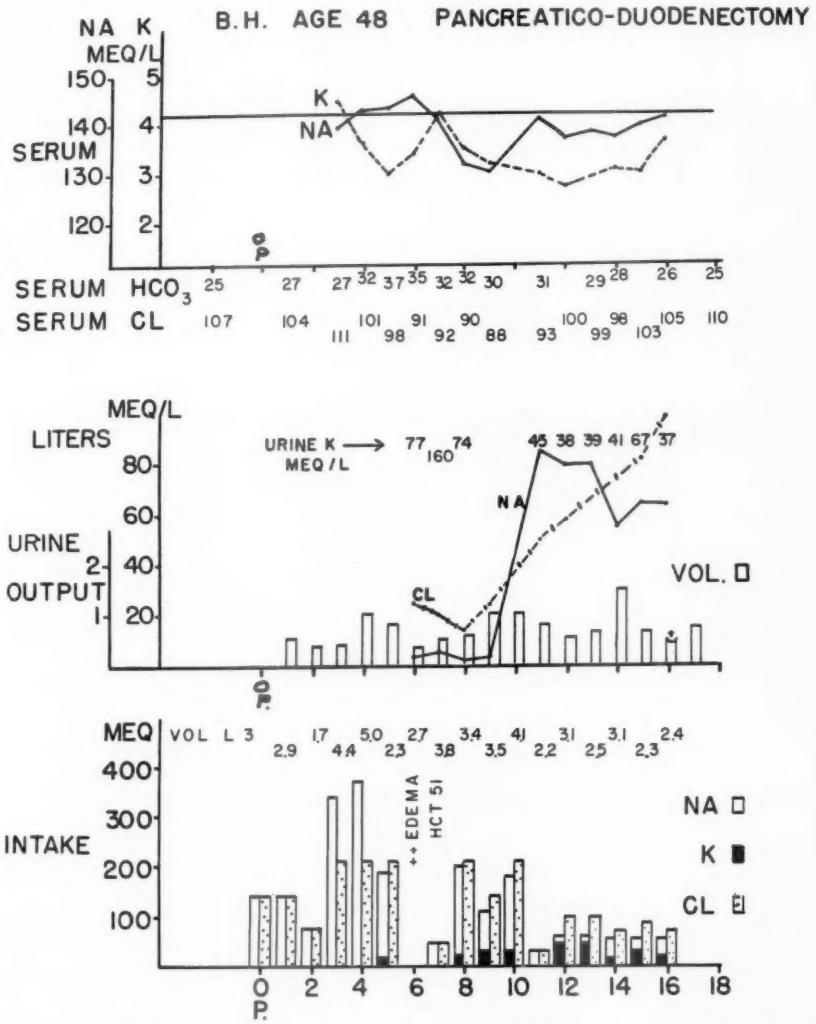

Fig. 2.—Early postoperative dehydration with excessive sodium administration, followed by edema and oliguria. Marked urinary sodium and chloride retention with sudden release on the tenth day.

Acute Sodium Retention With Low Urinary Sodium and Chloride Excretion.—Two cases in which serum electrolyte values were normal to high and in which postoperative renal sodium retention played a large part are illustrated in contrast to the previous cases.

B. H., a 48-year-old woman, entered the Presbyterian Hospital Sept. 21, 1948, with a chief complaint of generalized pruritis of four months' duration, painless jaundice of two and one-half months' duration, and a twenty-one pound weight loss. Diagnostic work-up revealed slight hepatomegaly and chemistries compatible with biliary obstruction, and positive stool

tests for occult blood with negative gastrointestinal x-ray studies. The abdomen was explored, and a carcinoma of the ampulla of Vater was found. A pancreaticoduodenectomy was done on Oct. 21, 1948.

Fig. 2 illustrates pertinent points in the postoperative course. Because of a high hematocrit, 60, and considerable wound drainage and vomiting and with relatively normal serum chemistries, she was given large volumes of saline solution and sodium lactate on the third and fourth postoperative days. It was not until she became edematous on the sixth

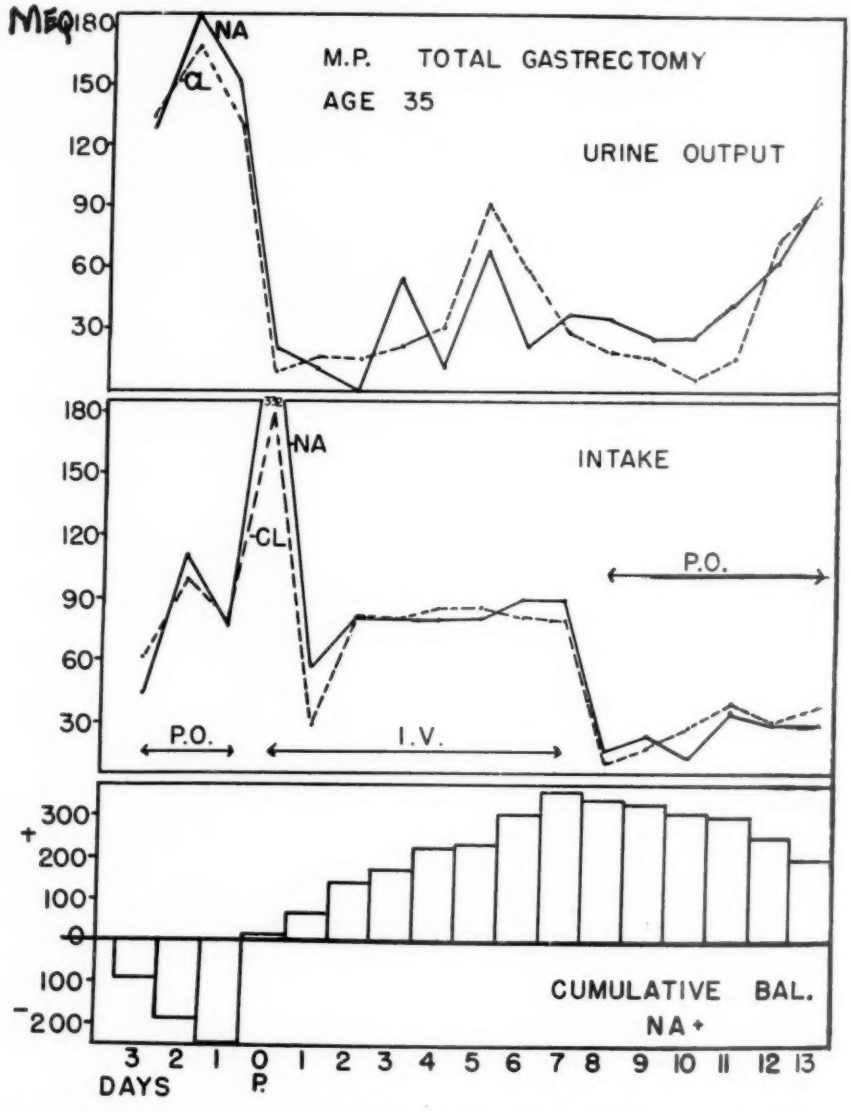

Fig. 3.—Low urine sodium and chloride output with sodium retention; patient on 500 c.c. of isotonic saline solution per day postoperatively.

postoperative day, still with an elevated hematocrit, that it was appreciated that she was excreting virtually no sodium with low normal urine chlorides. Subsequently from the sixth through the ninth day, nasogastric suction was used to decompress her stomach and remove electrolytes as well. When serum values fell below normal on the eighth and ninth days, some intravenous sodium, potassium, and chloride were given. The sharp break in urine values

between the ninth and eleventh days is interesting when compared to plasma values, as is the ratio of Na to Cl in the urine. Her convalescence was long, but she was well, without evidence of recurrence, on Jan. 15, 1950.

M. P. was a 34-year-old woman on whom a total gastrectomy was done following unsuccessful portocaval shunt for repeated hematemeses from esophogeal varices due to portal hypertension secondary to cavernous transformation of the portal vein. Fig. 3 shows total urine sodium and chloride output per day, daily intake of sodium and chloride ion, and cumulative sodium balance. It illustrates sodium retention from the first to seventh day, when an average of only 550 c.c. of saline solution was given a day, together with low postoperative urine sodium and chloride values.

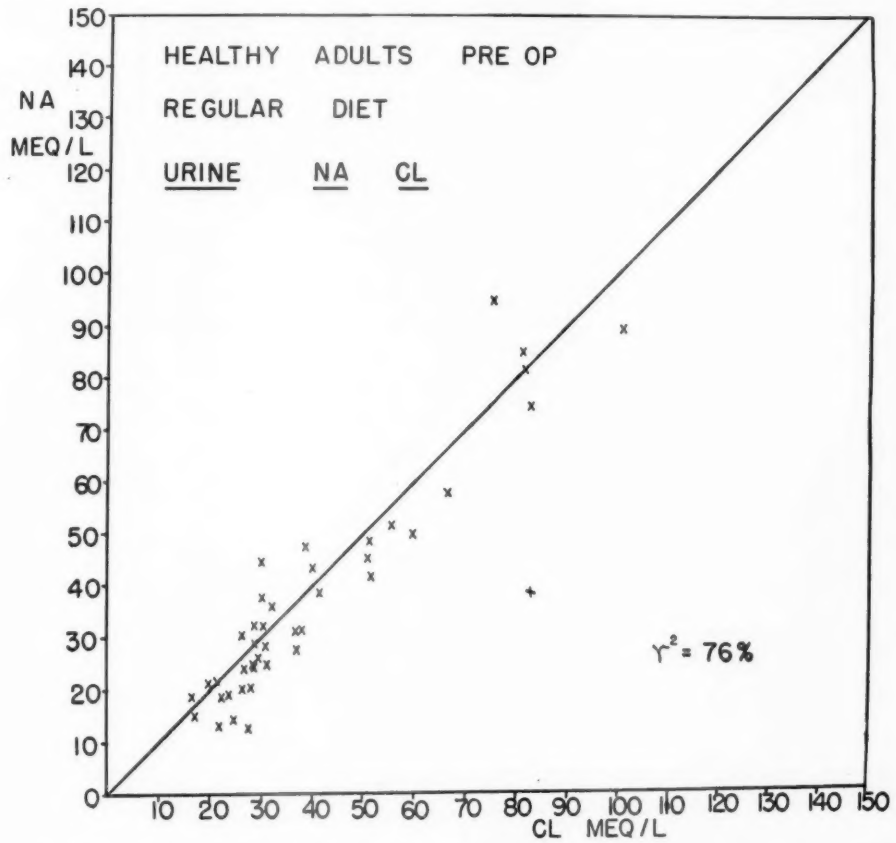

Fig. 4.—Group 1 patients on diet preoperatively. Urine sodium and chloride values (twenty-four hour pools). The oblique line indicates perfect correlation of sodium and chloride ions at different concentrations.

Urine Sodium and Chloride Excretion Under Controlled Metabolic Conditions.—Two groups of patients studied in the metabolism unit are presented to demonstrate base line urine sodium and chloride excretion and the effects of intravenous fluids and operations of a relatively minor variety on the ratio of urine sodium and chloride. These are the same patients discussed in our paper[23] on potassium deficiency and consist of five patients (M. M., C. C., A. C., M. B., and G. S.) in Group 1 and four patients (S. A., A. R., J. B., and M. B.) in Group 2. There were three ventral herniorraphies, one umbilical herniorraphy, and one cholecystectomy in the first group, and four cholecystectomies, one with drainage of the common duct, in the second. All but one were women.

Both groups received parenterally a fluid regimen giving an average of 50 c.c. per kilogram per day with 85 Gm. protein equivalent (13.5 Gm. of nitrogen as 10 per cent amino acids*) and a caloric total of 18 calories per kilogram. This regime was begun three days preoperatively after a ten-day period on a constant analyzed diet, and was carried through the operative day and for four days thereafter, when oral intake was resumed.

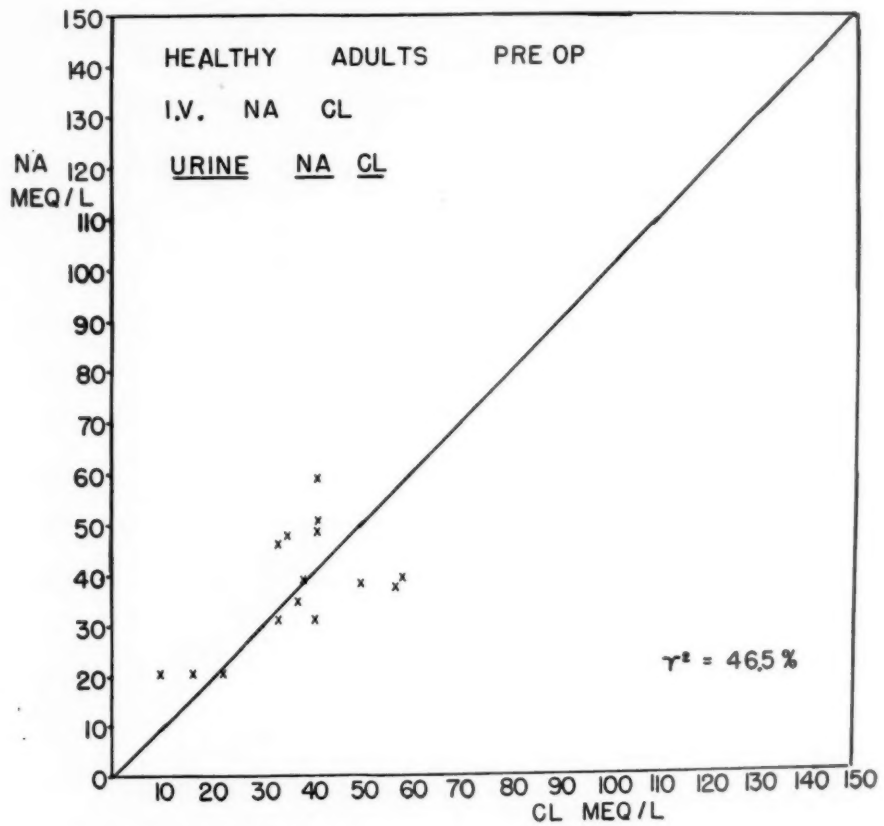

Fig. 5.—Group 1 patients on intravenous fluids preoperatively. Urine sodium and chloride values.

The two groups differed essentially only in that the second received 50 meq. of K per day while the first received no potassium. Average intakes for Group 1 were 145 meq. Na per day and 132.6 meq. Cl per day, while Group 2 received 151 meq. Na, 160 meq. Cl, and 50.7 meq. K daily.†

In the first group, during the control period on diet (Fig. 4), a high degree of correlation was seen to exist between urinary sodium ion concentration and that of the chloride ion. Food analyses indicated that the average diet contains a sodium to chloride ratio of 9 to 10, and this was reflected in the fact that the urinary output was slightly weighted in favor of chloride. The diagonal line

*Ten per cent amino acids were provided by Merck & Company, Inc., Rahway, N. J.

†Patients A. R., J. B., and M. B. in Group 2 received in addition an average of 55 meq. of HPO_4 per day while on parenteral fluids, while Patient S. A. received no HPO_4. A full report will be made of phosphate balance studies, but this amount had slight, if any, effect on potassium balance.

represented perfect correlation of sodium to chloride and was the relationship to be maintained if sodium were to be calculated from chloride measurements. The coefficient of determination was 76 per cent, a high degree of correlation.

When the patients were placed on intravenous fluids preoperatively (Fig. 5), the urine sodium to chloride ratios became more dispersed, and the coefficient of determination fell to 46.5 per cent. Note that the rather large volumes of fluid (50 c.c. per kilogram) resulted in lower concentrations of urine electrolytes.

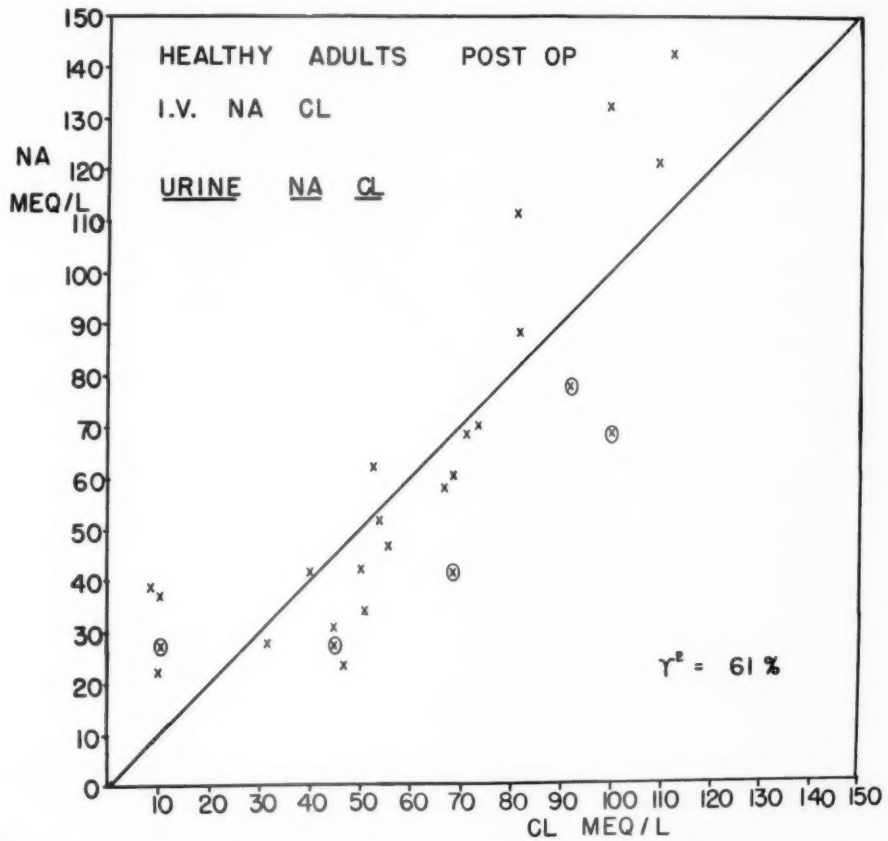

Fig. 6.—Group 1 patients operative day and postoperatively on intravenous fluids. Urine sodium and chloride values.

During the day of operation and the first four postoperative days (Fig. 6), the urinary chloride excretion exceeds the sodium by a small margin despite the fact that the sodium intake exceeded the chloride by 12.4 meq. per day (due to the small amounts of sodium used in buffering the amino acid preparations). In this connection, a comparison with the potassium group postoperatively (Fig. 9) showed that this tendency to hold sodium is much less evident when potassium is administered. Correlation remains quite good with $r^2 = 61$ per cent.

Group 2, which received parenteral potassium, showed a very similar control diet pattern to the first; chloride ion was slightly in excess of sodium ion excretion, and correlation was high with $r^2 = 86.5$ per cent (Fig. 7).

When placed on intravenous fluids (Fig. 8), this group also showed a slight increase in the dispersion of the urine sodium to chloride ratios, and r^2 dropped to 64 per cent. In the postoperative period (Fig. 9) one patient (S.A.) had drainage of bile from the T tube with loss of sodium in excess of chloride, and demonstrated compensation by excreting normal chloride concentrations with virtually no sodium on two days postoperatively. Aside from this, the behavior of the sodium to chloride ratios was virtually the same as in the first group. Correlation was $r^2 = 49.5$ per cent.

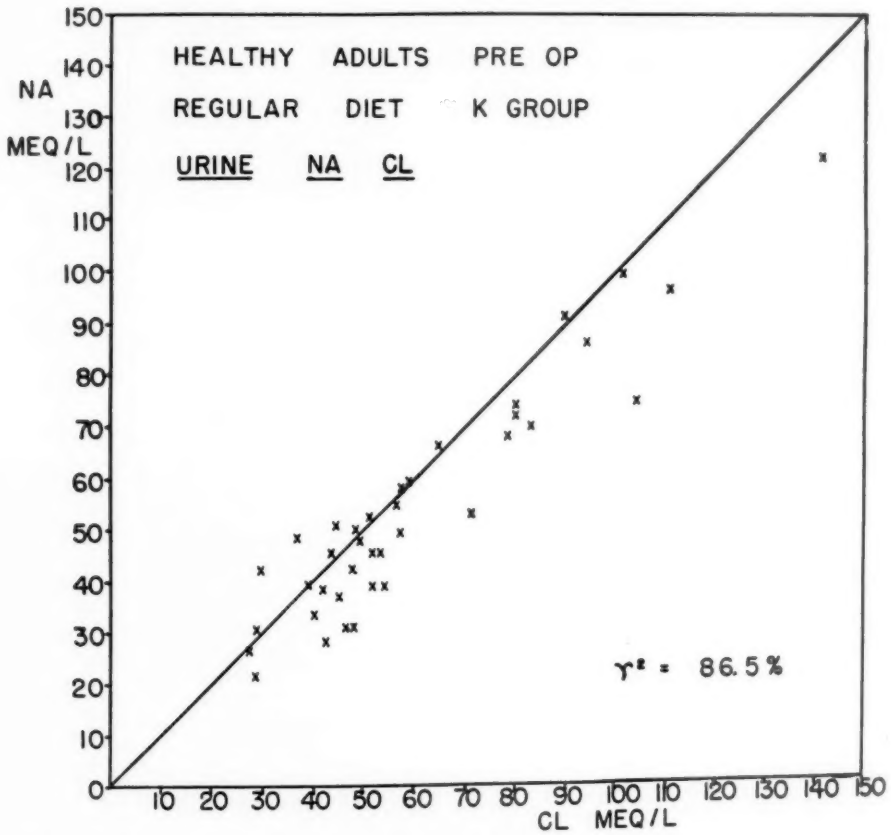

Fig. 7.—Group 2 patients on diet preoperatively. Urine sodium and chloride values.

The third and fourth groups represent peptic ulcer patients studied in the metabolic unit and differ from each other in that those patients in Group 3 were not obstructed and were on an ambulatory ulcer diet preoperatively, while those in Group 4 had pyloric obstruction. Of the obstructed group (Group 4) Patients X, O, B, and S had nothing by mouth, while patient A was on clear fluids, Patient C was on an ambulatory ulcer diet and vomited occasionally, and Patient M was on parenteral fluids until three days preoperatively, when the obstruction was relieved and he was placed on a soft diet.

In general, these patients received 140 to 180 meq. of Na and 160 to 210 meq. of Cl ion per day, with 60 meq. of K, and all but Patient C were given 57 meq. of HPO_4 for four days preoperatively in parenteral fluids. While the

patients were on oral intake, the analyzed electrolyte content of the diet was about one-half of the aforementioned intake, except for the phosphate, which was higher. Only Patient S had a marked chloride deficiency with severe alkalosis, and she was given an average of 150 meq. extra chloride ion per day for three days as NH_4Cl. Preoperatively all of Group 4 had been vomiting at some time while in the hospital, and all were aspirated at night for gastric residual. Patient S had marked alkalosis upon admission, with serum Na 135 meq., K 1.8 meq. with marked weakness, Cl 65 meq., and HCO_3 42 meq. She had a high gastric acidity with Cl of 100 to 120 meq. per liter and Na 40 to 60 in an average of 1,500 c.c. gastric loss per day. All plasma values returned to normal with five days' preoperative treatment. To our surprise, at operation she was found to have ulcerated prepyloric carcinoma. The others were not as

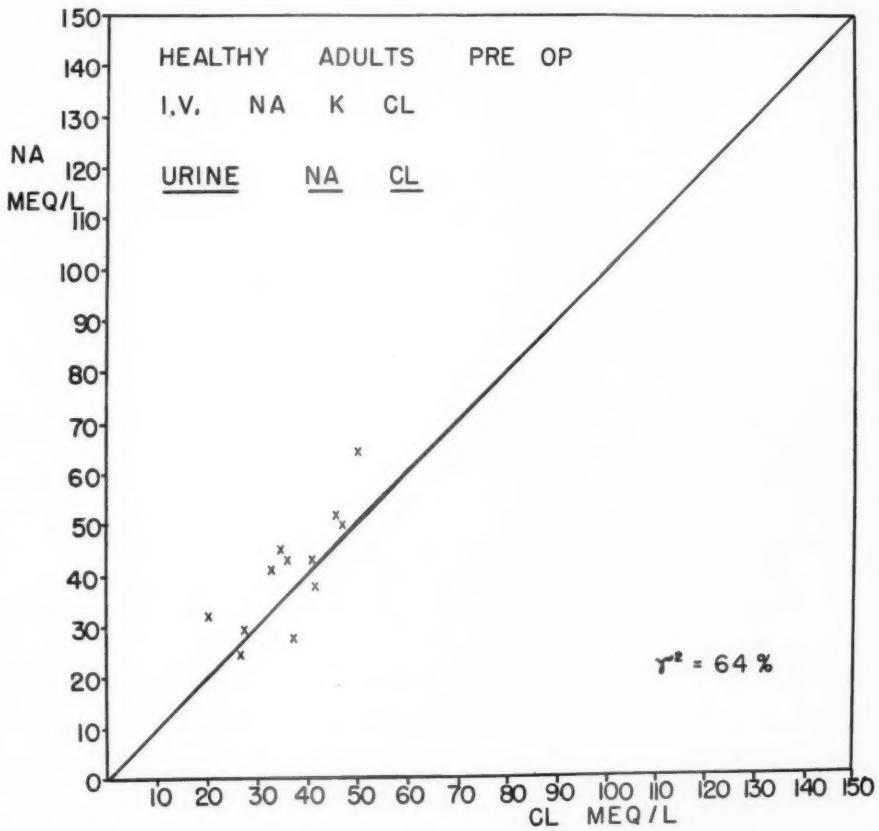

Fig. 8.—Group 2 patients preoperatively on intravenous fluids including potassium. Urine sodium and chloride values.

badly unbalanced, with average plasma Na 137.7, K 4.4, Cl 95.8, and HCO_3 27.4 meq. per liter on admission and Na 139, K 4.3, Cl 100.2, HCO_3 24.0 meq. per liter immediately preoperatively. Postoperatively on the third day their plasma values averaged Na 138.3, K 3.9, Cl. 100.9, and HCO_3 24.8 meq. per liter.

Postoperatively both groups were on tea, broth, water, and ginger ale by mouth on the third postoperative day and full liquid diet on the fourth day. Patients M, P, and S of the obstructed group (Group 4) received between 150

and 200 meq. of Na and Cl ions the first and second postoperative days; the rest received from none to a maximum of 73 meq. of each. The patients of the unobstructed group (Group 3) all received 140 to 160 meq. of sodium and chloride the first and second day and none thereafter, except Patient K, who received these levels for four days. Fifty-seven meq. of HPO_4 were given daily

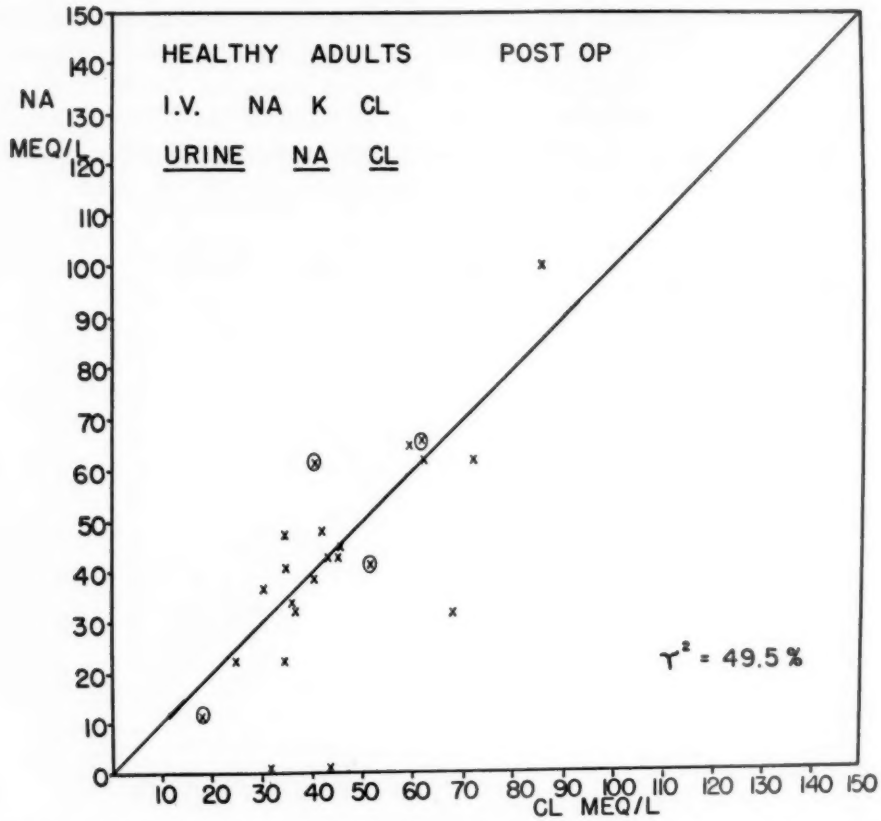

Fig. 9.—Group 2 patients operative day and postoperatively on intravenous fluids including potassium. Urine sodium and chloride values.

to Patients C, G, and K per day while on parenteral fluids with 60 to 65 meq. of K. Figs. 10 and 11 show the urine sodium and chloride ratios in Group 3 pre- and postoperatively. Preoperatively the patients were on the wards an average of only three days, and their varied intakes and use of proprietary alkaline preparations before entering the hospital are reflected in their urine outputs, $r^2 = 51$ per cent.

Postoperatively, with more uniform intake and closely parallel progress, the correlation of urine sodium to chloride rose and actually was somewhat better than the postoperative periods of Groups 1 and 2: $r^2 = 74$ per cent. Possible reasons for this will be discussed.

Group 4 presented a striking contrast (Figs. 12 and 13) to the previous three groups in urine sodium to chloride ratios. The rate of sodium excretion far exceeded that of the chloride, as expected with predominating chloride ion loss from the stomach, and correlation fell markedly, $r^2 = 26$ per cent. Post-

operatively (Fig. 13), despite the fact that sodium chloride intake was limited to prevent sodium retention and serum Na, K,Cl, and HCO_3 levels remained essentially unchanged, there was a significant shift in the excretion ratio, chloride ion dominating markedly during the average of eight days postoperatively in which observations were made. Sodium to chloride correlation was low with $r^2 = 23.6$ per cent.

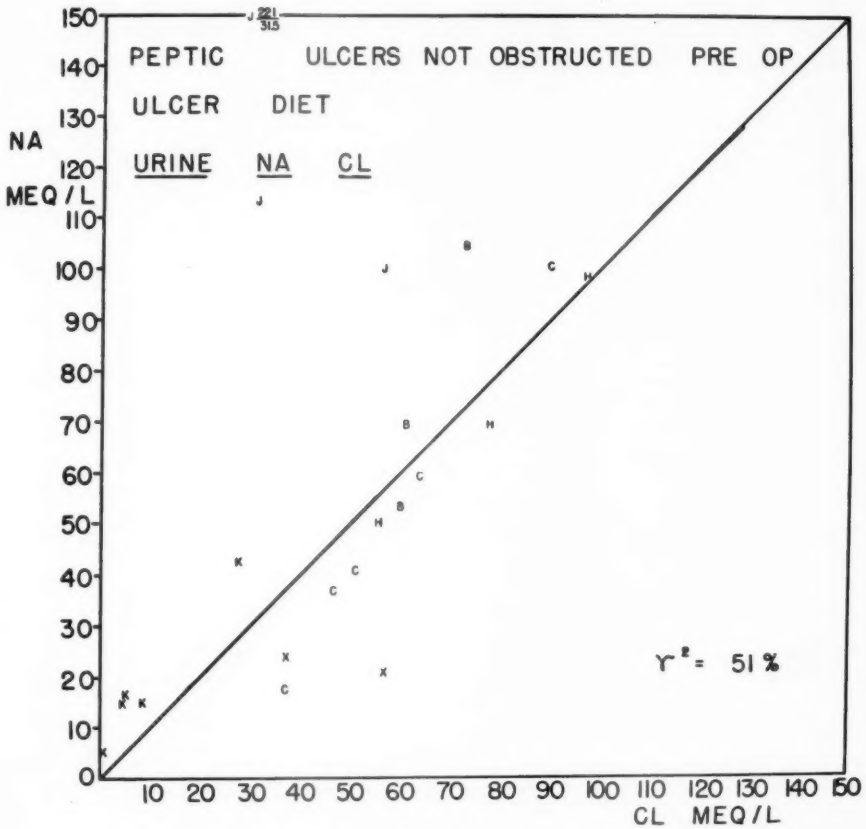

Fig. 10.—Group 3 patients preoperatively on soft diets. Urine sodium and chloride values.

Two cases illustrate some of the daily variations in urine sodium to chloride ratios.

G. S., a 43-year-old woman with cirrhosis of the liver but without ascites, and with normal plasma protein, had a history of bleeding from esophageal varices. A portal vein to vena cava shunt was performed, and Fig. 14 illustrates the daily sodium and chloride urine excretion. The ratio of 60 meq. of Cl to 12.4 meq. of Na per liter on the second postoperative day contrasted sharply with a Cl of 10 meq. and a Na of 77 meq. per liter on the ninth postoperative day. Because of the well-known tendency of cirrhotic patients to become edematous postoperatively and to hold sodium, the patient was given no parenteral Na or Cl and took in an average of 45 meq. of Na and 39 meq. of Cl orally in diet starting the fifth postoperative day.

J. D. was a 58-year-old man with a thirty-one year history of gastric ulcer symptoms. The ulcers had perforated in 1920. He was nearly symptom-free from 1921 until August, 1949, when he began again to have persistent epigastric pain, and x-ray examination

revealed a duodenal ulcer with a high degree of twenty-four hour retention in an atonic stomach. Prior to admission he had had two months of marked increase in symptoms with occasional vomiting. Shortly after admission he suddenly went into shock, with muscular twitchings and hyperirritability, unconsciousness, and low blood pressure. Hematocrit was 53, plasma Na 140, K 5.6, Cl 37, and HCO_3 more than 42 meq. per liter. He was treated with sodium and ammonium chloride at first, and later potassium chloride as well, with gradual recovery. He was oliguric at first, and, despite increasing urine volume, blood urea nitrogen continued to rise rapidly until the fourth day, when it gradually began to fall. Urine Na and Cl levels together with plasma levels are shown in Fig. 15. Note that at the point where hematocrit reached a low point and serum values were above normal in both sodium and chloride that the urine chloride excretion barely reached 50 meq. per liter and that it was considerably below the sodium. There was no gastric loss during this entire period.

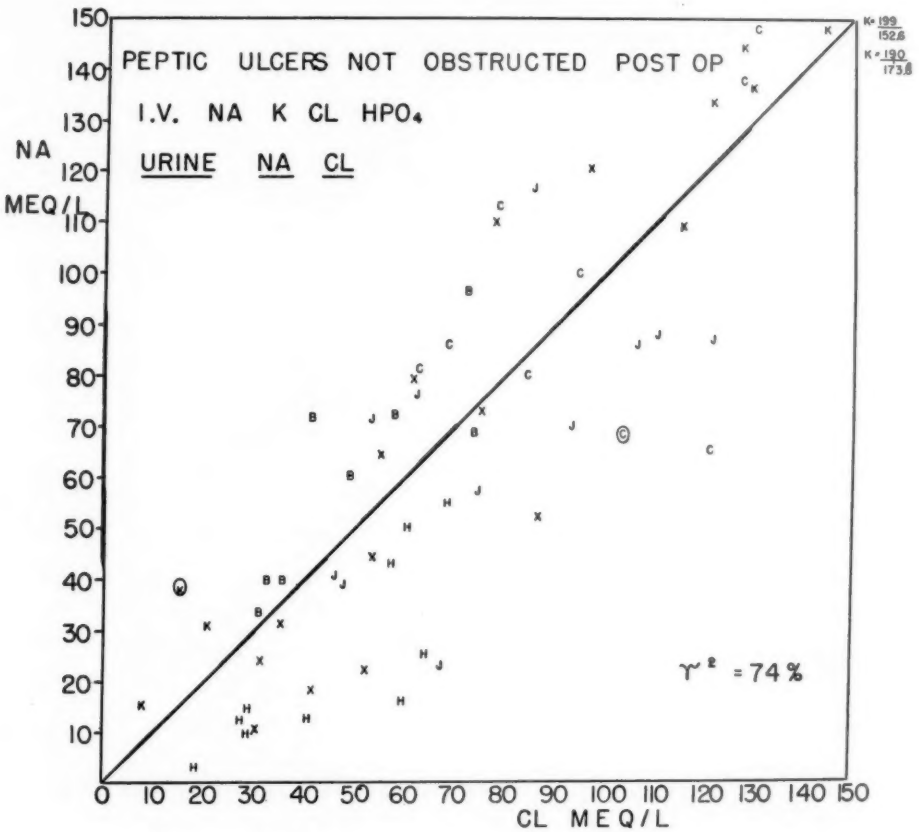

Fig. 11.—Group 3 patients postoperatively. Urine sodium and chloride values.

Fig. 16 shows the urine sodium and chloride ratios in the first week postoperatively for fourteen patients who had undergone major surgery on the general service (Group 5). This group included three pancreaticoduodenectomies, four small bowel obstructions, an emergency gastrectomy for bleeding duodenal ulcer following a Roux-type plastic procedure on the common duct, another ulcer with alkalosis and dehydration, a sigmoid obstruction, a pericardiectomy, a mesenteric thrombosis, a gastrojejunocolic fistula, and a pancreatic abscess following acute pancreatitis. Only the patient with mesenteric thrombosis died. The degree of correlation between urine sodium and chloride was obviously very low, and r^2 was 23.6 per cent.

DISCUSSION

Sodium Deficiency and Retention.—The first group consisted of patients with generalized peritonitis. It is widely known that generalized peritonitis, like trauma and extensive burns, produces a rapid and massive depletion of the extracellular fluid as water, extracellular electrolytes, and plasma protein leak through damaged capillaries into the peritoneal cavity. This sudden creation of a third fluid space makes immediate demands on extracellular fluid and indirectly on intracellular fluid. This loss, if not rapidly replaced, results in peripheral vascular collapse from internal dehydration and sodium and chloride

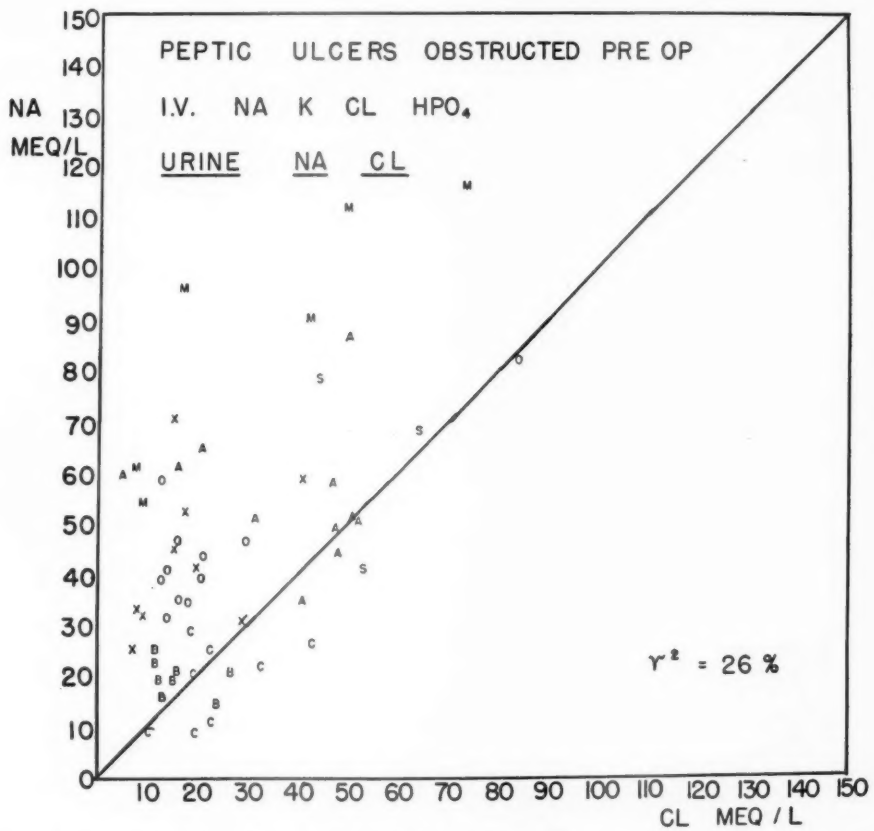

Fig. 12.—Group 4 patients postoperatively. Urine sodium and chloride values. See text for intakes.

depletion. The cases of patients M. B. and B. H., briefly presented, illustrate the low levels of serum sodium found in such cases. The process may well be overwhelming in spite of vigorous therapy, as the case of M. B. illustrates. Hypertonic saline solution as advocated by Peters[9, 10] was indicated, but it is doubtful that it would have altered the outcome.

The cardiac group is particularly interesting in that this problem constitutes an increasingly large consideration in surgery in the older age groups. It is a natural tendency to withhold sodium in cardiac hypertensive patients in borderline failure as in C. W. and J. H., yet serious consequences resulted in

both cases, and fatalities might well have occurred had not serum sodium levels revealed that dehydration was accompanied by even greater electrolyte depletion, for it is this combination which Elkinton, Danowski, and Winkler[5] demonstrated which is responsible for most peripheral vascular collapse.

The case of J. H. (Fig. 1) is presented in considerable detail and illustrates the effect of withholding saline solution postoperatively in a 76-year-old hypertensive cardiac patient, who, as the result of probably preexisting low sodium levels and some "third space effect" from operative trauma, became rapidly dehydrated postoperatively with a low serum sodium level. Note that

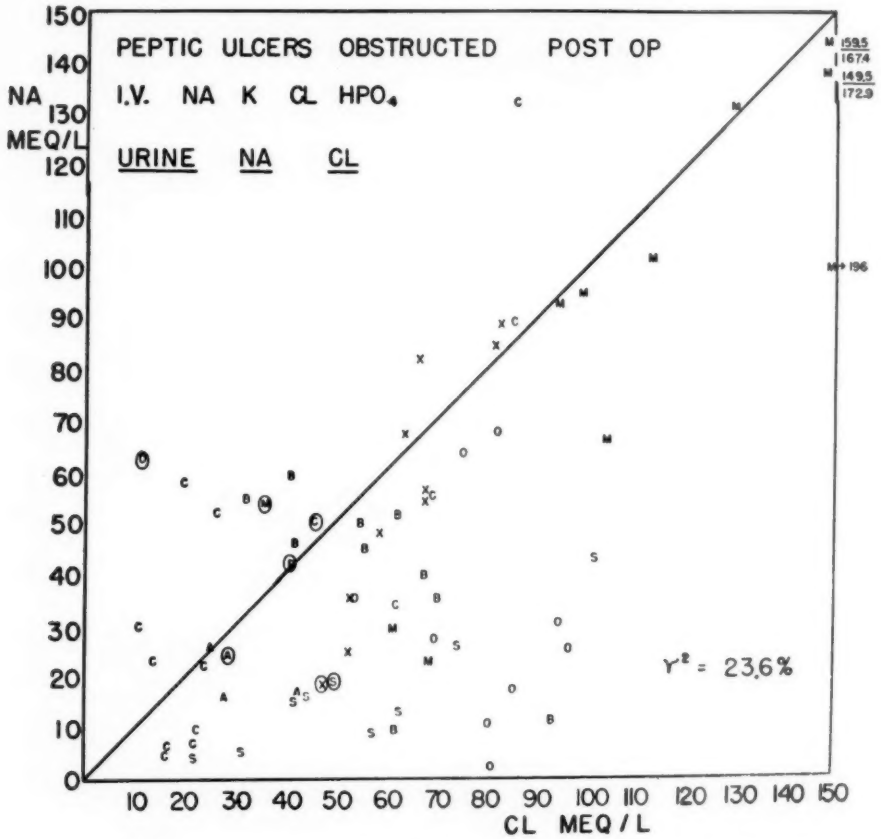

Fig. 13.—Group 4 patients postoperatively. Urine sodium and chloride values.

she retained about 7,000 c.c. of 11,000 c.c. given her the third, fourth, and fifth postoperative days, allowing 800 c.c. per day for insensible loss. There was no secondary diuresis, and serum levels remained in low normal range so that both the water and the 1,100 meq. of Na must have been in absolute deficit.

The case of M. L. demonstrates that a young woman can go into frank cardiac failure after receiving fairly large volumes of fluid postoperatively with relatively little sodium and chloride ion. Her moderately severe hypoproteinemia (4.32 Gm. total protein on the third postoperative day) and edema certainly suggested an overexpanded extracellular fluid volume, and the low

protein is compatible with that reported by Elkinton, Danowski, and Winkler,[5] and Abbott[24] in salt depletion. She was digitalized, given increased amounts of sodium and chloride ion parenterally and a total of 175 Gm. of albumin. It may be that digitalis alone would have been sufficient. The albumin was given to raise temporarily the plasma osmotic pressure to mobilize water for renal excretion and thereby concentrate extracellular electrolytes. The fact that urine Na was 6 meq. and Cl 7 meq. per liter during her diuresis suggests that sodium and chloride ion deficits played an important part in the picture of circulatory failure, for had she had too much sodium it would have been excreted at this time.

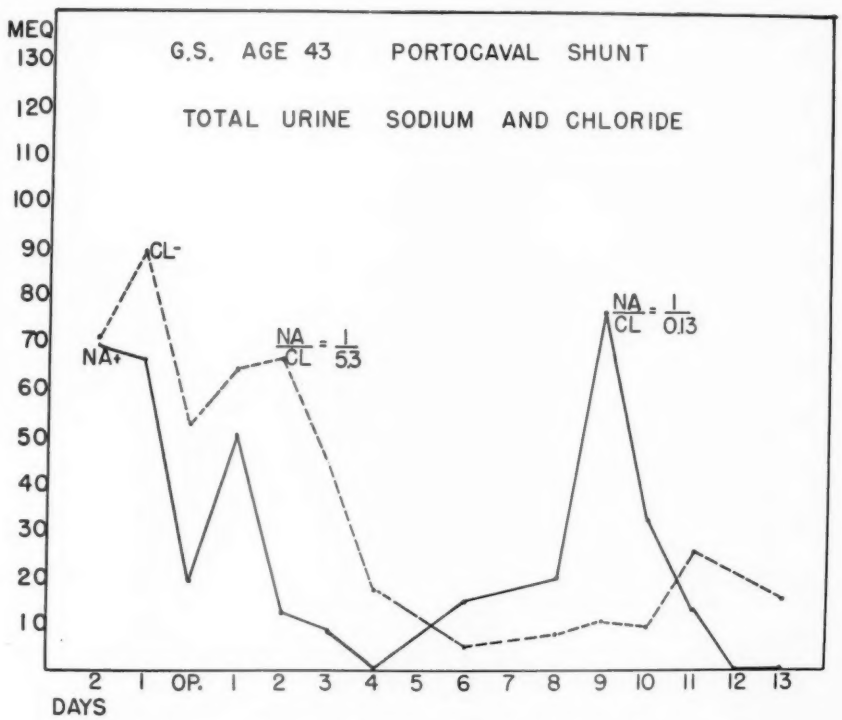

Fig. 14.—Variations in urine sodium and chloride ratio postoperatively.

Marked loss of sodium in recent ileostomies with development of acute deficiency is reported by Cave[25] and is now a well-recognized syndrome. We have found that analysis of the sodium, potassium, and chloride losses from ileostomies when volumes are large, together with quantitative replacement of losses, is essential to the recovery of these patients.

The fourth group of patients in which we have seen low serum sodium levels is the now widely recognized class of patients with large volumes of loss from the intestinal tract and those with biliary and pancreatic fistulae. The wide range in electrolyte concentrations in these fluids and the average losses per liter are discussed in a previous paper.[26] The necessity of keeping accurate balance sheets and doing daily analyses of sodium, potassium, and chloride ion

in plasma, urine, and drainages, together with quantitative replacement of deficits, in patients with large volumes of fluid exchange cannot be overemphasized.

As Coller[11, 12] has emphasized, the surgical patient is also subject to the hazards of excessive sodium chloride administration, particularly in the immediate postoperative period when urinary excretion of sodium and chloride may

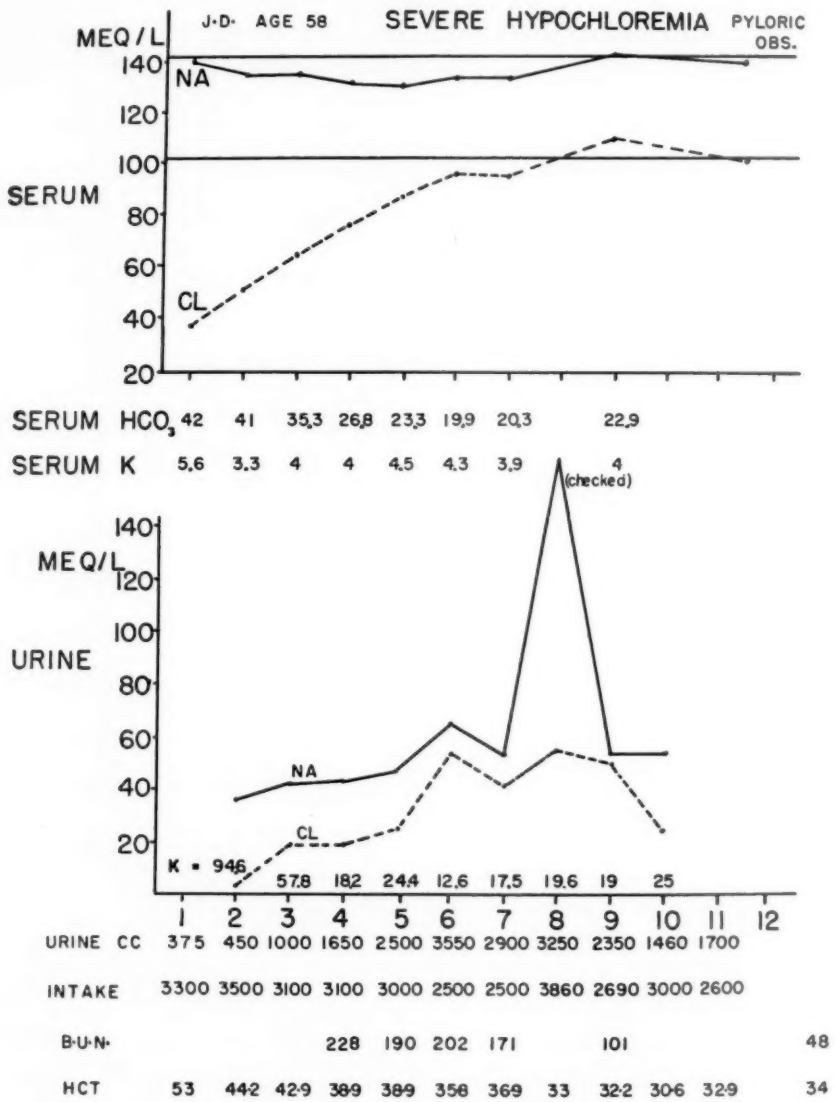

Fig. 15.—Severe hypochloremia due to pyloric obstruction. Dehydration with normal serum sodium concentration. Treated with sodium, potassium, and ammonium chlorides.

be minimal despite a satisfactory urine volume. It is of vital importance to distinguish between this reaction, which is now attributed to adrenal cortical hyperactivity in response to trauma, and during which very little or no sodium chloride should be administered if there are no other losses, and the situation seen in Patients M. L. and J. H. (Fig. 1) where a sodium deficit existed.

Patients B. H. (Fig. 2) and M. P. (Fig. 3) illustrate sodium retention together with low urinary excretion levels of sodium and chloride. In the case of Patient B. H., immediately postoperatively she was given 3, 2.9, and 1.7 L. of parenteral fluids, yet became markedly dehydrated, with a hematocrit of 60 and low urine volume. She was accordingly given larger volumes of fluid with sodium chloride and sodium lactate in an endeavor to re-expand her extracellular fluid compartment. She then became edematous with a still somewhat

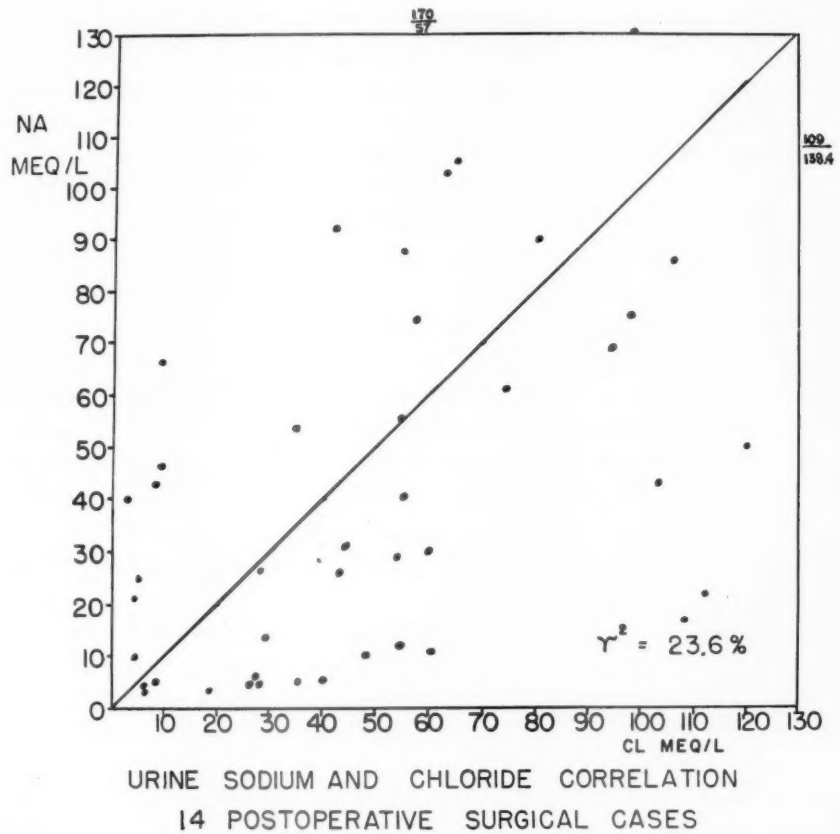

Fig. 16.—Fourteen major postoperative cases showing urine sodium and chloride ratios during the first postoperative week.

elevated hematocrit, normal serum sodium, and slightly low serum chloride. Urine values were found to be extremely low in both sodium and chloride, and it became apparent that additional sodium and chloride would only aggravate the situation. Accordingly, only dextrose in water was given, and then as serum sodium levels fell and nasogastric tube drainage became large, the nasogastric suction loss was merely replaced quantitatively. On the tenth postoperative day there was a sudden change in urine sodium and chloride excretion without significant diuresis, and her edema slowly disappeared.

In M. P. (Fig. 3) is illustrated the amount of sodium retention on 500 c.c. of saline solution a day given subsequent to a total gastrectomy. Serum levels in this patient remained normal throughout, but it was not until she was placed on oral intake with virtually no sodium that her positive balance

began to decline. Had she been given large volumes of saline solution because of her low urinary excretion rate of electrolytes, she certainly would have become edematous.

Urine Electrolyte Evaluation.—Experiences with such problems as the foregoing, together with reports in the literature by Fantus,[14] Van Slyke and Evans[15] and Bryant[16] on using urine chloride as a method of estimating sodium chloride need or excretion, led us to evaluate the urine sodium and chloride excretion in several of our metabolic study groups in an effort to determine of what value urine electrolyte concentrations, particularly that of chloride ion, might be in replacement therapy. We were also interested to find what relationship the urine chloride concentration might bear to urine sodium concentration.

TABLE I. GRAMS OF SODIUM CHLORIDE FROM FANTUS TEST AND CALCULATED FROM SODIUM AND CHLORIDE DETERMINATIONS IN URINE

	1	2	3	4	5
	GM. NaCl	Cl	Na	Na	Cl
SPECIMEN	FANTUS	AS GM. NaCl	AS GM. NaCl	MEQ. PER LITER	MEQ. PER LITER
1	2	3.8	3.0	52.6	70.5
2	1	0.1	0.1	1	0.9
3	5	3.6	3.8	65.0	62.6
4	4	4.1	4.1	70.7	73.6
5	2	0.6	6.5	112.8	10.8
6	2	0.9	1.2	20.8	16.6
7	3	2.3	0.05	1	42.0
8	1	0.1	0.05	1	0.9
9	4	3.8	6.0	103.0	70.6
10	5	4.2	1.9	32.5	75.0
11	5	5.1	2.8	47.8	93.0
12	9	12.3	5.9	101.5	210.0
13	3	1.9	1.6	28.0	32.4
14	2	1.6	4.1	69.5	27.7
15	1	0.2	2.8	48.5	3.2
16	2	0.3	1.2	20.0	4.2
17	5	4.3	4.5	76.0	74.5
18	3	1.4	2.4	41.0	23.2
19	4	3.5	2.8	47.0	59.8
20	3	2.8	3.2	54.0	48.2
21	6	4.6	8.0	138.0	79.3
22	4	3.3	3.3	56.5	56.2
23	3	2.0	1.3	22.0	34.8
24	5	3.4	3.8	65.6	59.0
25	7	5.6	3.6	61.0	95.2
26	5	3.0	5.4	92.0	51.2
27	4	2.3	2.0	35.1	39.3
28	6	6.3	5.8	99.8	108.3
29	2	1.9	2.0	34.0	33.0

We endeavored to correlate the Fantus test[14] with urine chloride as determined by the Schales and Schales titration[21] and also to correlate sodium determined from chloride as sodium chloride with actual determinations with the flame photometer. Table I shows the results obtained on twenty-nine consecutive urines sent to the laboratory for analysis. It shows fair correlation of the Fantus and Schales and Schales chloride (Columns 1 and 2) and much poorer correlation for sodium (Columns 1 and 3). Actual values are shown in Columns 4 and 5.

Groups 1 and 2 included patients who had relatively atraumatic procedures. In Group 1 (Fig. 4) preoperative urine sodium and chloride values on con-

trolled diet have a high correlation. When these patients were placed on intravenous fluids (Fig. 5), the correlation dropped significantly. Intravenous fluid therapy itself produces marked changes in potassium balance [23, 28, 29, 30] and apparently affects the ratio of urine sodium to chloride as well. Postoperatively the correlation improved only slightly (Fig. 6).

Patients in group 2 had 50 meq. of K per day intravenously and showed a pattern similar to Group 1. Preoperatively (Fig. 7) correlation was high, fell with intravenous fluid therapy (Fig. 8), and fell slightly more postoperatively (Fig. 9). The two very low sodium values were in Patient S. A., who lost sodium in excess of chloride from bile drainage. It is interesting that sodium conservation is so complete with relatively normal chloride excretion.

Groups 3 and 4 present a more striking contrast. The patients in group 3 preoperatively were on the ward only two to three days, and their individual diets were varied. Some had been taking proprietary alkaline preparations for their ulcer symptoms before admission. Their preoperative urine values are quite scattered. (Fig. 10). Postoperatively (Fig. 11), on a uniform regime and with closely parallel uncomplicated courses, their urine sodium to chloride correlations rose, although there was considerable variation in concentration.

Group 4 patients (Fig. 12) all had obstructions preoperatively, but, as is noted, they had nearly normal plasma levels of Na, K, Cl and HCO_3, with the exception of Patient S, who was in alkalosis and was given extra chloride ion as NH_4Cl. All except Patients B and C excreted far more sodium than chloride in their urine, and relative chloride retention suggests a larger chloride deficit than was obvious from plasma levels.

Postoperatively (Fig. 13) there was a surprising reversal, with chloride excretion far exceeding sodium, and Patients B and C again showing the least shift. Sodium to chloride correlation was poor in both pre- and postoperative phases with a reversal of the discrepancy.

A day-by-day analysis of postoperative output ratio is shown in Patient G. S. (Fig. 14) and attention is called to the marked reversal of sodium and chloride ratios comparing the second and ninth days.

In Patient J. D. (Fig. 15), who presented the most marked case of hypochloremia that we have recorded to date, the urine sodium exceeded the chloride throughout the entire period of observation, even after serum levels had exceeded normal for chloride and suggested some lag in adjusting to compensated blood levels. Note that the urine Cl level was 50 meq. per liter when plasma Cl was 110 meq. on the ninth day. Urine potassium levels fell in concentration as urine volume increased, and the serum urea nitrogen fell only slowly. The data suggest definite renal injury, probably as the result of the alkalosis.

Group 5 patients (Fig. 16) represent a collection of sodium and chloride determinations on fourteen major cases during the first postoperative week. All of these patients were seriously ill, and the low degree of correlation between urine sodium and chloride is very evident. In no way could the urine chloride be taken as an index of urine sodium excretion. Van Slyke and Evans[15] and Coller and DeWeese[27] warned that only in the presence of normal renal function and adequate output could urine chlorides be used as an index for sodium chloride replacement.

Our data suggest that in the sick surgical patient there is usually sufficient metabolic imbalance so that urine sodium to chloride correlation is very poor, and further that there is often sufficient postoperative sodium retention and to a lesser extent chloride retention so that urine values of chloride ion concentration are a poor guide to chloride requirements, and a totally unreliable and potentially dangerous index to sodium requirements.

It is more than ever evident that the management of major surgical problems involves consideration of each individual case as an entity. Adequate fluid and electrolyte therapy demands the ready availability of accurate determinations of plasma, urine, and drainage electrolyte concentrations so that replacement and maintenance may be accomplished quantitatively to meet the varying requirements of each patient.

CONCLUSIONS

Sodium deficiency states in surgical patients on a general service were seen in acute peritonitis, in patients with hypertension and cardiac failure, in acute ileostomies, and in patients with large fluid losses from the gastrointestinal tract with inadequate electrolyte replacement. In all groups the adequate replacement of sodium and chloride deficits is imperative. The incidence of these acute derangements of electrolyte balance has markedly diminished since electrolyte determinations have become routine with preoperative correction.

Postoperative sodium and chloride retention was also observed, with edema, hemoconcentration, and oliguria appearing with excessive sodium administration; the importance of distinguishing between retention and sodium deficiency is emphasized.

Urine sodium to chloride ratios were analyzed in five groups of surgical patients. The correlation of urine sodium to chloride on regular diets preoperatively is high in normal patients, decreases significantly when these patients are placed on intravenous fluids preoperatively, and changes relatively little with operation. Patients who had potassium intravenously had somewhat lower postoperative correlation than those that had not. In two groups of patients with peptic ulcers subjected to partial gastrectomy, postoperative urine sodium to chloride correlation was high in unobstructed cases, but in obstructed peptic ulcers, despite normal plasma sodium, potassium, chloride, and HCO_3 levels preoperatively, preoperative urine contained far more sodium than chloride while the reverse was true postoperatively, and correlations were poor.

A group of seriously ill patients after major surgery showed poor correlation of urine sodium and chloride excretion.

Methods of estimating sodium and chloride excretion and replacement by measurement of urine chlorides alone in major surgical cases are inadequate and may be dangerous. Quantitative determinations of individual ions in blood, urine, and drainages are essential if the patient is to be kept in fluid and electrolyte balance.

Acknowledgment.—This work would not have been possible without the valuable assistance of the nursing and technical staff of the surgical metabolic unit, including Miss Florence Schorske, Miss Rita Lipton, Miss Emily Cragin, Mrs. Hilda Carter, Miss Helen Pandelakis, Miss Charlotte Richardson, Miss Edith Rosenblad, and Miss Dorothy Lee.

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DISCUSSION

DR. JONATHAN E. RHOADS.—I would just like to say that this represents an exceedingly laborious study and I think it has finally laid to rest for us the hypothesis that one can handle surgical patients by following the urine chloride excretion.

This concept has cropped up again and again in the discussion of some of our colleagues. The great quantity of data presented in this paper shows how exceedingly fallacious such a concept is. It ought to answer once and for all the arguments in favor of such a practice.

DR. J. LOCKWOOD.—I was glad to have Dr. Rhoads' comment. I think there is a very important practical lesson here. The so-called bedside Fantus test provides a very satisfactory basis for calculating sodium chloride requirements in the individual who is not particularly sick. Confronted with a really severe problem of dehydration or shift of electrolytes or fluids from one compartment to another, the test begins to lose its usefulness precisely where we need it most.

We have begun to feel now that in the management of the occasional very severe problem of dehydration with excessive drainage or loss, there is no substitute whatsoever for the daily or even more often than once-a-day individual determination of quantities of sodium, potassium, and chloride being lost in drainage fluids and circulating in the serum.

As a matter of fact, we have begun to project some of our experimental studies in the field of quantitation, because we feel an obligation now to prevent these distortions in balance, which formerly appeared without our anticipating them. Now that we can and do anticipate them, it is becoming increasingly difficult to find suitable material for study of the more extreme imbalances.

Also I suspect that some of the postoperative difficulties we have formerly attributed to hypoproteinemia, let's say, or some other type of deficiency, have actually been due to our failure to recognize the severity of these electrolyte imbalances.

Although I am not by any means implying we are going to discard plasma protein concentrations, we are putting our primary attention in postoperative management of the severely sick patients on variations in the red cell mass and on variations in the base factors, and with that primary emphasis I believe we are making real progress in reducing the postoperative morbidity and mortality of some of our patients.

EXPERIMENTAL TUBERCULOSIS

I. Effects of Anastomosis Between Systemic and Pulmonary Arteries on Tuberculosis in Monkeys

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FOR many years there have been sporadic attempts to modify the course of human pulmonary tuberculosis by altering the pulmonary circulation. Our interest in the subject has been stimulated by Dock's[1] hypothesis that apical localization of tuberculosis is the result of inadequate arterial blood flow through the upper one-third of the lung.

Very few investigations of the effects of circulatory alterations on experimental tuberculosis have been carried out. Tiegel,[2] in 1911, studied the effects of venous congestion in the lungs on pulmonary tuberculosis in dogs and rabbits. He found that venous stasis afforded protection against the disease induced by intravenous inoculation. A decade later Schlaepfer[3] reported his observations on ligation of a pulmonary artery in normal animals and suggested that pulmonary artery ligation be given clinical trial in patients with tuberculosis.

A small number of tuberculous patients have been subjected to ligation of a pulmonary artery by Wilms,[4] Eloesser[5] and Rienhoff.[6] A few others have been treated by partial occlusion of the pulmonary veins by Edel,[7] Kerschner,[8] and O'Shaugnessy.[9] In one case described by Babcock,[10] anastomosis between the carotid and jugular vessels was carried out with the hope of relieving the work of the lung in advanced tuberculosis. The results of these varied clinical procedures are difficult to assess from available reports.

We have undertaken a systematic investigation of the effects of circulatory alteration on pulmonary tuberculosis. This report is concerned with the effects of anastomosis between systemic and pulmonary arteries in monkeys with experimentally induced tuberculosis.

METHODS

In these experiments 36 healthy Macaca mulatta monkeys weighing 9 to 16 pounds were used. All were selected from carefully segregated stock animals which had shown consistently negative reactions to repeated tuberculin tests.

Each animal was injected intravenously (saphenous vein) with a standard suspension of a virulent human strain of *Mycobacterium tuberculosis.* The intravenous route of inoculation was chosen in order to effect approximately equal seeding of the 2 lungs with tubercle bacilli.

The day after inoculation a number of the monkeys were submitted to thoracotomy. In the majority of these animals anastomoses were carried out between systemic and pulmonary arteries. In several animals an end-to-end

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anastomosis was done between the subclavian or innominate artery and the distal end of a divided pulmonary artery. In others the proximal end of the innominate artery was joined to the side of the right pulmonary artery. More than one-half of the total number of injected monkeys were set aside as unoperated controls, while control thoracotomies were done in 2 animals and the exposed lung packed down for 1 hour to simulate operative conditions during the anastomosis.

BACTERIOLOGIC TECHNIQUE

A virulent human strain of *Myco. tuberculosis* isolated by one of us (B.J.O.) at the National Institutes of Health was used in these experiments. The virulence of this strain for guinea pigs and DBA mice is illustrated by the death curves given in Fig. 1. These curves are typical of those obtained with this strain during the period in which these experiments were conducted.

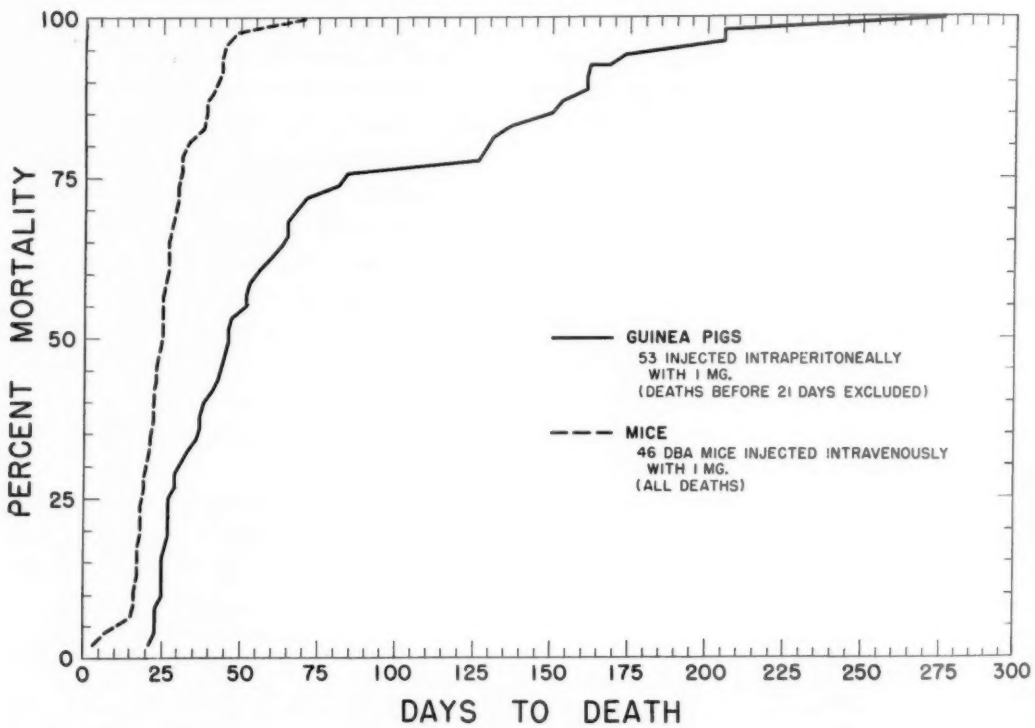


Fig. 1.—Virulence of strain 198-ARB for guinea pigs and DBA mice. These death curves are typical of those obtained with this strain throughout the 18 month period in which the experiments with these monkeys were conducted.

Since its isolation the culture has been grown on an inspissated egg medium similar to that described by Frimodt-Möller*[11] with subculture at 2 week intervals. An emulsion of this culture (13 to 17 days old) is prepared for injection in the following manner: The growth is removed from the egg slant with a stiff nichrome wire loop taking care to avoid the inclusion of the nutrient medium. The growth is weighed and is transferred to a ball mill. The mill consists of a 1 L. balloon flask containing 18 c.c. of saline solution and approximately 300 stainless steel balls one-fourth inch in diameter. This is rotated for 1 hour

*No malachite green was added.

in a White bacterial grinder at 56 r.p.m. After this period of grinding sufficient saline solution is added to produce a concentration of 5 mg. of organisms per cubic centimeter. The grinding is continued for 45 minutes, after which the concentration is adjusted to 1 mg. of organisms per cubic centimeter.

Each monkey is given intravenously a 1 c.c. dose of a 1:10,000 dilution of this suspension. Measured gravimetrically this dose is 10^{-4} mg. As may be seen in Table I, the number of injected viable particles (single or clumped bacilli) varied from 53 to 158. The method of determining the actual number of viable particles injected is as follows: The suspension containing 1 mg. of organisms per cubic centimeter is diluted to yield concentrations of 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} of the original. From each of the 4 dilutions 0.2 c.c. amounts are planted over the surface of each of 10 selected slants of the inspissated egg medium. These cultures are left overnight in a slanted position. The following day they are capped and placed in the incubator. After 3 weeks and at weekly intervals thereafter until the seventh week, the developing colonies on each slant are counted. From these data the number of viable particles in the original suspension can be estimated. Table I gives the dose for each animal in respect to milligrams of moist weight and plate count.

Every effort has been exerted to insure uniformity in different preparations of emulsions during the 18 month period in which these animal inoculations were made.

OPERATIVE TECHNIQUE

Intravenous sodium pentobarbital anesthesia (30 mg. per kilogram) with morphine-atropine premedication was used. Pulmonary ventilation was maintained by means of a mechanical respirator which delivered oxygen through an endotracheal tube.[12] Aseptic surgical technique was used in all operations.

After the hair had been clipped from the operative area, the skin was painted with tincture of iodine followed by alcohol. The chest was entered anteriorly through the fourth intercostal space on the left or right. The pulmonary artery to the exposed lung was dissected free. After the innominate artery on the right or the subclavian artery on the left had been isolated and occluded proximally with a rubber-shod clamp, it was ligated distally and divided. The adventitia was cleaned from the end of the systemic artery before it was placed in apposition to the pulmonary artery.

The anastomosis was carried out following the technique of Blalock.[13] In an end-to-end union the right or left pulmonary artery was ligated deep in the mediastinum near the main pulmonary trunk, occluded distally with a rubber-shod clamp, and divided between the ligature and the lung. The proximal end of the systemic artery was then sutured to the distal end of the pulmonary artery with a continuous everting mattress suture of 000000 arterial silk on an atraumatic needle.

In an end-to-side anastomosis the right pulmonary artery was occluded proximally and distally with rubber-shod clamps. An appropriate incision was placed in the anterosuperior aspect of the pulmonary artery and the proximal end of the innominate artery was anastomosed to the side of the pulmonary

TABLE I. EXPERIMENTAL DATA IN MONKEYS GIVEN TUBERCLE BACILLI INTRAVENOUSLY 18 TO 24 HOURS BEFORE OPERATION

MONKEY NUMBER	OPERATIVE PROCEDURE (ANASTOMOSIS)	DOSAGE OF TUBERCLE BACILLI (MG.)	PLATE COUNT OF DOSAGE (VIABLE PARTICLES)	SURVIVAL TIME (DAYS P.O.)	AUTOPSY FINDINGS		
					LUNGS	OTHER ORGANS	LUNG WITH GREATER INVOLVEMENT
3	Left subclavian to end left pulmonary	10^{-4}	158	96	Large conglomerate caseous masses and multiple 1 to 2 cm. tubercles in left lung; fine miliary tubercles in right lung	Large caseous masses in liver, spleen and nodes; fine miliary in other viscera; brain and meninges negative	Operative side
2	Left subclavian to end left pulmonary	10^{-4}	158	184	Left lung hemorrhagic; solid caseation of left middle lobe and left lower lobe, caseous 1 cm. lesions in left upper lobe; right lung smaller than left; few 1 to 2 mm. lesions in right middle lobe and right lower lobe, many 3 to 5 mm. lesions in right upper lobe	Many 2 cm. caseous abscesses in spleen; scattered fine miliary in liver and other viscera; brain negative	Operative side
1	Left subclavian to end left pulmonary	10^{-4}	158	257	Diffuse caseous consolidation of lower and middle lobes of both lungs; 4 cm. caseous abscess in mediastinum ruptured into trachea with bronchial drainage into both lungs	2 to 3 cm. caseous lesions in spleen; fine miliary in liver and other organs; brain and meninges negative	No difference
5	Innominate to end right pulmonary	10^{-4}	137	110	Right lung 3 to 4 × size of left; massive caseation of entire right lung; scattered 1 to 4 mm. lesions in left lung	Mediastinal nodes large and caseous; scattered miliary lesions in viscera; brain negative	Operative side
4	Innominate to end right pulmonary	10^{-4}	137	118	Right lung showed many 2 to 3 cm. caseous masses; few scattered 1 to 2 mm. tubercles in left lung; single 0.5 cm. caseous lesion left middle lobe	Multiple 0.5 cm. caseous lesions in spleen, liver, kidneys, nodes; miliary in other organs; brain and meninges negative	Operative side

E-26	Innominate to end right pulmonary	10-4	108	95	Right lung larger than left; multiple 0.5 cm. caseous lesions throughout right lung, solid caseation right middle lobe; scattered fine miliary lesions in left lung	Spleen completely caseous; 1 cm. lesions in liver; 0.5 cm. lesions in mesentery; scattered miliary in other organs; brain negative	Operative side
H-13	Innominate to end right pulmonary	10-4	99	80	Right lung larger than left; closely packed 3 to 15 mm. caseous lesions in right lung with diffuse caseation of right middle lobe; much smaller and less numerous tubercles in left lung	Spleen, liver, nodes contain 1 to 10 mm. lesions; no gross lesions elsewhere; brain negative	Operative side
H-12	Innominate to end right pulmonary	10-4	99	92	Right lung 1½ × size left; numerous closely packed, 5 to 15 mm. caseous lesions in right lung with 3 cm. caseous masses in right middle lobe and right lower lobe; fewer and smaller tubercles in left lung	Spleen, liver, nodes, pancreas contain many 2 to 10 mm. caseous lesions; scattered miliary in other organs; brain and meninges negative	Operative side
H-20	Innominate to end right pulmonary	10-4		108	Right lung 1½ × size left; right lung filled with 2 to 3 cm. conglomerate caseous masses; fewer, scattered, 2 to 5 mm. caseous tubercles in left lung	Spleen, liver, nodes, pancreas contain closely packed 5 to 12 mm. caseous lesions; scattered miliary in other organs; brain negative	Operative side
27	Innominate to side right pulmonary	10-4	53	79	Right lung 1½ × size left; many 2 to 3 cm. conglomerate caseous masses in right lung; fewer, 0.5 to 1 cm. caseous lesions in left lung	Spleen, liver, nodes contain 0.5 to 1 cm. caseous lesions; scattered miliary in other organs; brain negative	Operative side
E-20	Innominate to side right pulmonary	10-4	53	262	Right lung 1½ × size left; 6 cm. caseous abscess in right upper lobe and 2.5 cm. caseous mass in right lower lobe; scattered 3 to 5 mm. caseous lesions in left lung	Spleen completely caseous; liver, nodes contain 1 cm. caseous lesions; scattered miliary in other organs; brain negative	Operative side
D-20	Innominate to side right pulmonary	10-4	53	81	Scattered 1 cm. caseous lesions and fine miliary tubercles equally distributed throughout both lungs	Spleen, liver, and nodes contain 0.5 to 1 cm. caseous lesions; scattered miliary in other organs; brain negative	No difference

artery with 000000 silk sutures. The conditions obtaining in end-to-end and in end-to-side anastomosis are depicted in Fig. 2.

After completion of the anastomosis the constricting devices were removed from the vessels and the mediastinal pleura was closed. The lung was carefully re-expanded and closure of the chest wall was carried out in layers with interrupted fine silk sutures.

In the 2 control thoracotomies the same technique was followed except that anastomosis was not performed. In these cases the lung was packed down with moist gauze for 1 hour after which it was carefully reinflated and closure of the chest wall was carried out.

Following operation each monkey received a single intramuscular injection of 300,000 units of penicillin in oil. The animals were kept in separate cages in the same isolation room and were fed stock diet until their deaths.

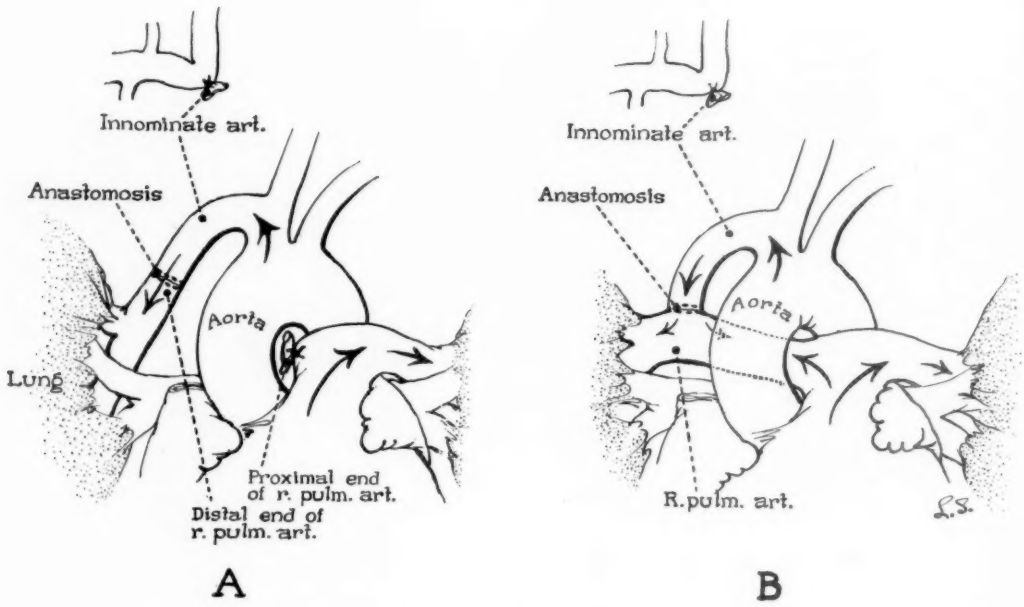


Fig. 2, *A* and *B*.—Diagrams of anastomoses used in these experiments. *A*, Anastomosis between proximal end of innominate artery and distal end of right pulmonary artery. (The left subclavian was used in the 3 end-to-end anastomoses to the left pulmonary artery). *B*, Anastomosis between proximal end of innominate artery and side of right pulmonary artery.

RESULTS

There were no immediate postoperative deaths in the 14 animals subjected to operation. All wounds healed *per primam* and there were no instances of wound infection or empyema. Tuberculosis developed in each of the 36 inoculated monkeys and the disease was allowed to progress to a fatal termination. Complete autopsies were performed immediately after death in each case. A special attempt was made to compare the character and extent of the tuberculosis in one lung with that in the other. Anastomoses were carefully examined for patency. Sections were taken from the lungs and other viscera for microscopic study. Color photographs were made as an aid to recording gross pathologic appearances.

End-to-End Systemic Pulmonary Anastomoses.—In 9 monkeys an end-to-end anastomosis was performed between a systemic and a pulmonary artery. In 6 of these animals the anastomosis was made between the proximal innominate artery and the distal right pulmonary artery. In 3 others the proximal end of the left subclavian artery was anastomosed to the distal end of the left pulmonary artery.

These monkeys lived from 80 to 257 days after inoculation. The autopsy findings are summarized in Table I. The arterial anastomosis was widely patent at the time of death in each of the 9 monkeys.

In 8 of the 9 animals with end-to-end anastomosis the extent of the pulmonary disease at autopsy was greater in the lung on the side of the anastomosis. Examples of this difference in the disease are depicted in Figs. 3, 4, and 5. There were numerous conglomerate tuberculous lesions in the lung on the side of operation. This lung showed massive caseous areas in contrast to the opposite lung, which presented smaller, less widely distributed tubercles. In most animals

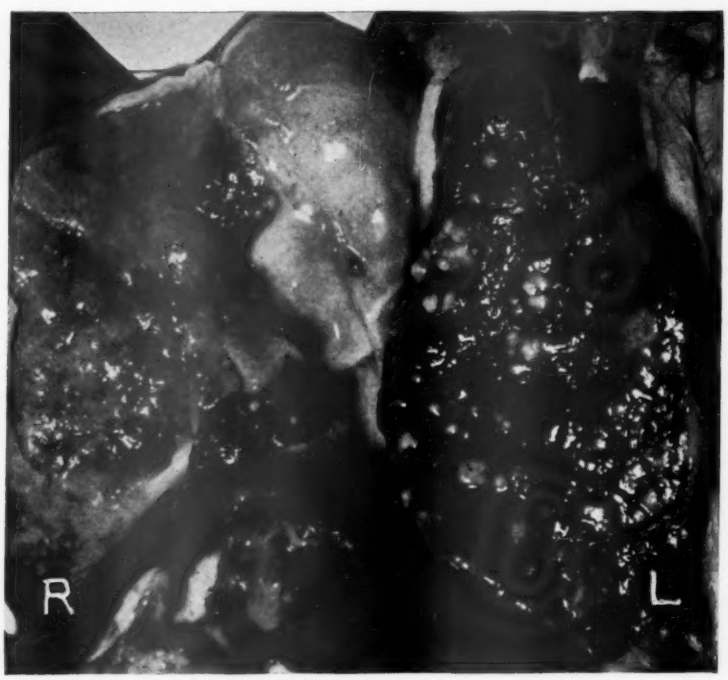


Fig. 3.—End-to-end anastomosis between left subclavian and left pulmonary artery. Photograph of diaphragmatic aspect of lungs showing greater involvement on left.

the lung on the side of the anastomosis was larger than the opposite lung. This increase in volume is largely attributable to the greater amount of caseous tuberculosis in the lung. Fig. 5 illustrates an extreme example of this change in pulmonary volume due to massive tuberculous infiltration.

In 1 monkey there was no apparent difference in the distribution or character of the lesions in the 2 lungs. This animal lived for 257 days after an end-to-end anastomosis between the left subclavian and the left pulmonary artery. Autopsy in this monkey showed a caseous mediastinal abscess which had ruptured

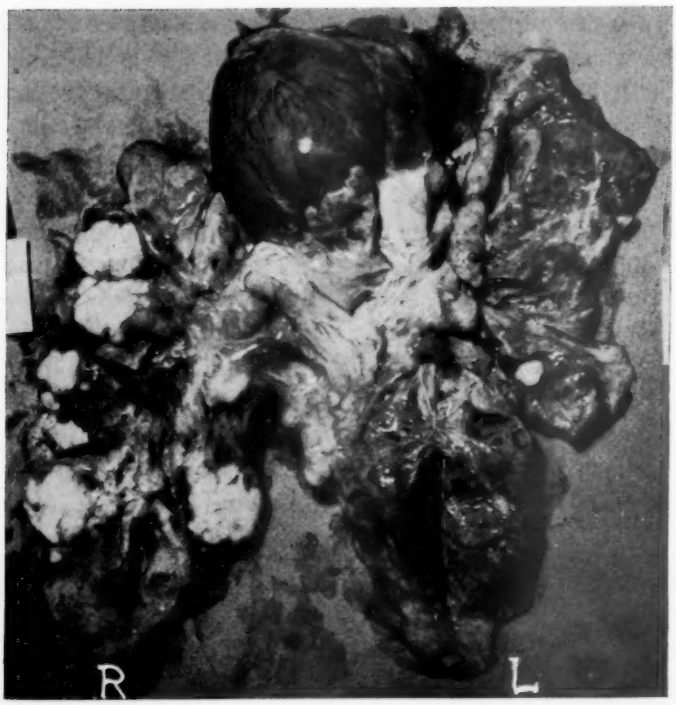


Fig. 4.—End-to-end anastomosis between innominate and right pulmonary artery. Photograph of sectioned lungs showing large caseous foci in right lung.

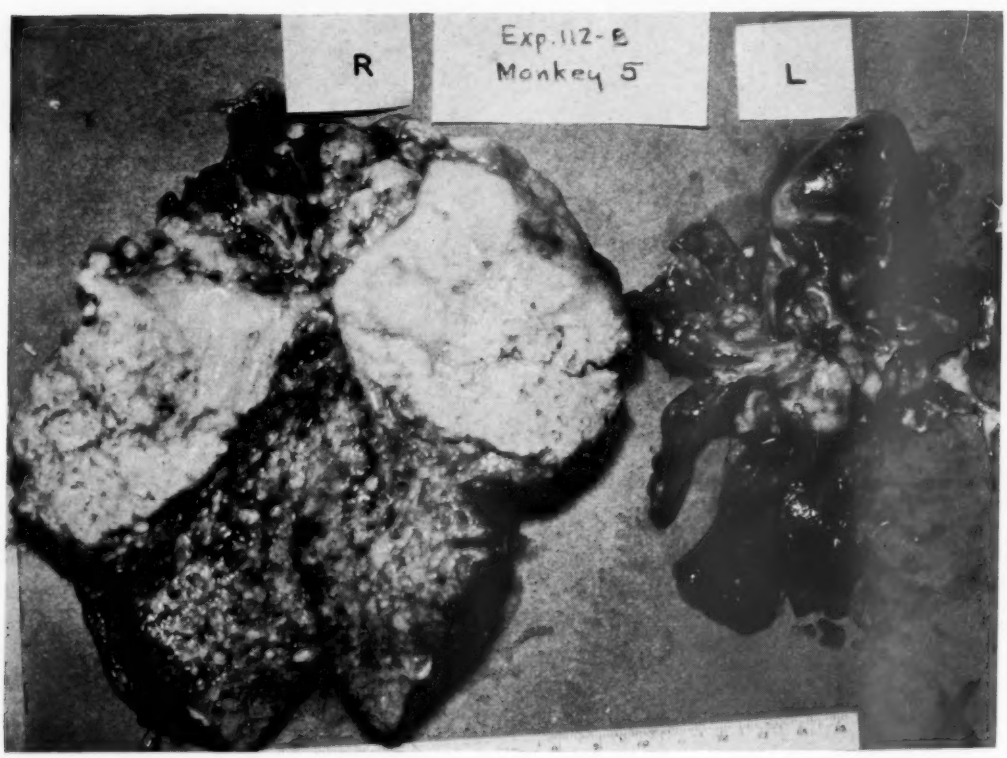


Fig. 5.—End-to-end anastomosis between innominate and right pulmonary artery. Photograph of lungs removed at autopsy. Right lung is tremendously enlarged and almost completely caseous. Heart is still attached to left lung which is air-containing and shows a few small tubercles.

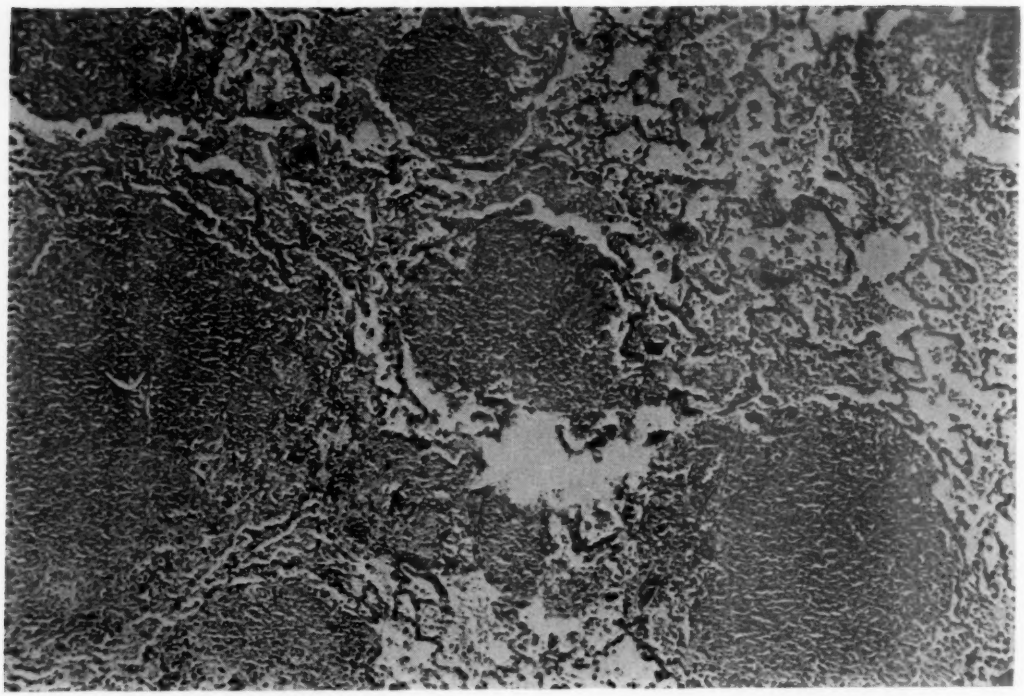
into the trachea just above its bifurcation, resulting in massive bronchial inundation of both lungs with caseous material. This accident appeared to have occurred a considerable time before death and may well have obscured any pre-existing differences in the extent of the disease in the 2 lungs.

The extrapulmonary lesions in this group of monkeys were concentrated chiefly in liver, lymph nodes, and spleen, although scattered miliary lesions were distributed throughout many other viscera. The brain and meninges were uninvolved by tubercles in these animals. Fig. 6 illustrates the lesions characteristically present in liver and spleen.

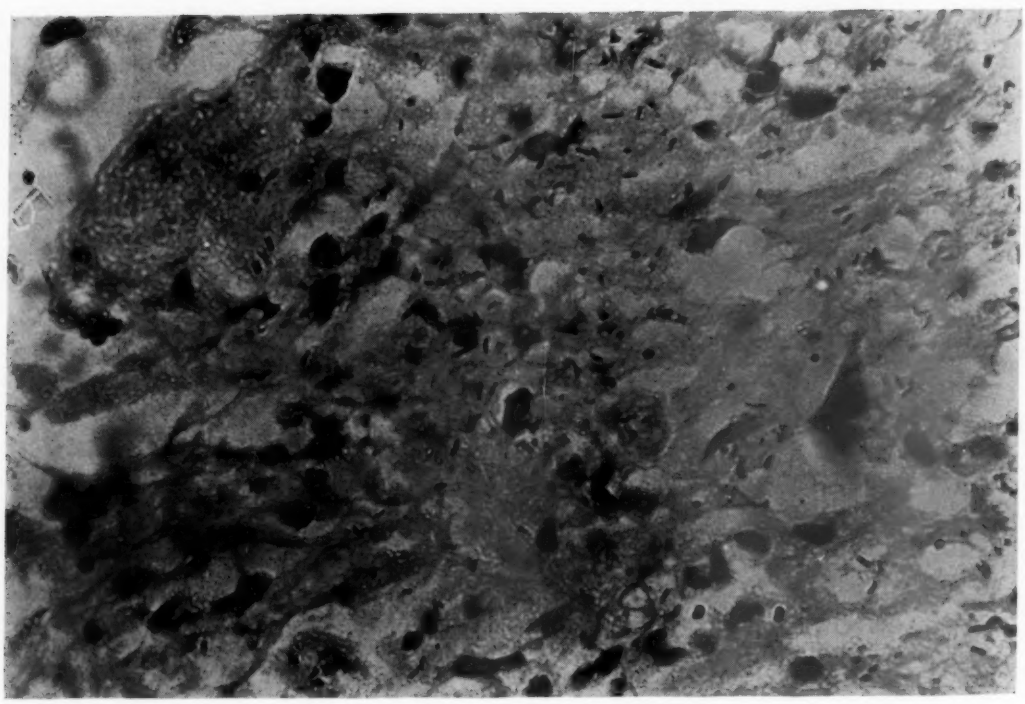
Fig. 6.—Photograph of abdominal viscera showing typical lesions in liver and spleen.

Microscopic study of sections from the lungs and other viscera of these monkeys confirmed the gross findings at autopsy. Acid-fast stains demonstrated large numbers of tubercle bacilli in the lesions. There was a uniform lack of fibrosis around the involved areas. Microscopic examination of the lesions in the 2 lungs failed to show any significant differences which were not apparent from the gross examination. A typical example of the microscopic picture of these pulmonary lesions is seen in Fig. 7.

End-to-Side Anastomoses Between Innominate and Right Pulmonary Arteries.—In 3 monkeys anastomosis was made between the proximal end of the innominate artery and the side of the right pulmonary artery. These animals lived for 79, 81, and 262 days. At autopsy the anastomosis was patent in each case. Caseous lesions were present in both lungs. In 1 animal the distribution was equal on the 2 sides. In the 2 remaining monkeys, however, the disease



A.



B.

Fig. 7.—*A*, Photomicrograph (×87) of lung with end-to-end anastomosis showing caseation with minimal fibrosis typical of the disease in these monkeys. *B*, Photomicrograph (×1000) showing acid-fast bacilli in one of these lesions.

process was much greater in the right lung (side of anastomosis) than in the left. Figs. 8 and 9 show the massive caseation of the right lung in 2 of these animals.

Extrapulmonary lesions in these 3 animals were concentrated in liver and spleen with only scattered fine miliary foci in other viscera. The character and distribution of these extrapulmonary lesions were similar to those in animals with end-to-end anastomosis.

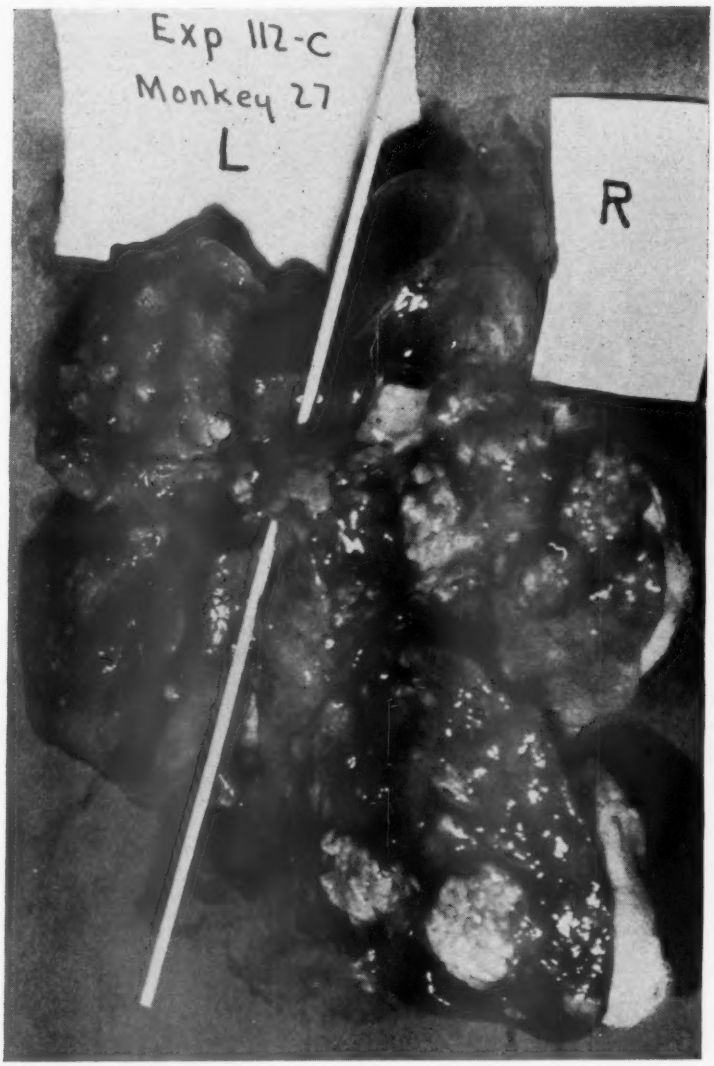


Fig. 8.—End-to-side anastomosis between innominate and right pulmonary artery. Photograph of lungs (dorsal view) showing caseous lesions bilaterally, more extensive on right.

Microscopic study of sections from the lungs confirmed the gross findings. Abundant tubercle bacilli were demonstrated in the lesions by acid-fast stains. A photomicrograph of a section of the right lung from 1 of these animals (Fig. 10) demonstrates the characteristic caseous necrosis with minimal fibrosis.

Controls.—As in the case of the monkeys subjected to operation, all of the control animals received an intravenous injection of 10^{-4} mg. of the same strain of tubercle bacilli. In 6 of these monkeys nothing further was done. In 2 other animals thoracotomy was performed, together with an amount of dissection comparable to that required for anastomosis, but no anastomosis was carried out. Sixteen additional animals which received the same dose of tubercle bacilli intravenously were available from a concurrent experiment at the National Institutes of Health. These 16 monkeys received orally a drug[14] which has

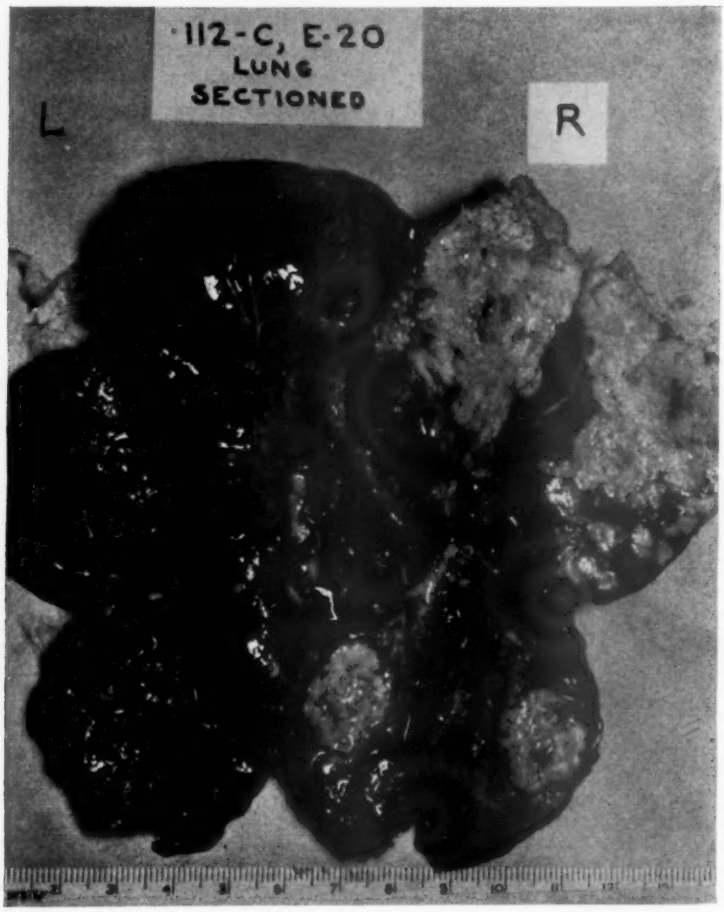


Fig. 9.—End-to-side anastomosis between innominate and right pulmonary artery. Photograph of sectioned lungs showing extensive caseous areas in right lung.

proved to have no effect on the distribution of tuberculosis in monkeys. Thus, a total of 24 monkeys served as controls for the distribution of tuberculous lesions in the 12 animals with anastomoses. These control animals died in 76 to 186 days with widespread tuberculosis.

Characteristically the tubercles were of miliary type, ranging from 1 to 5 mm. in diameter. In 19 of the 24 control animals the lesions were equal in size and number in the 2 lungs. Fig. 11 demonstrates the typical pulmonary findings at autopsy in 1 of these monkeys. In the 5 remaining animals the lesions were both larger and more numerous in 1 lung than in the other. This predominance

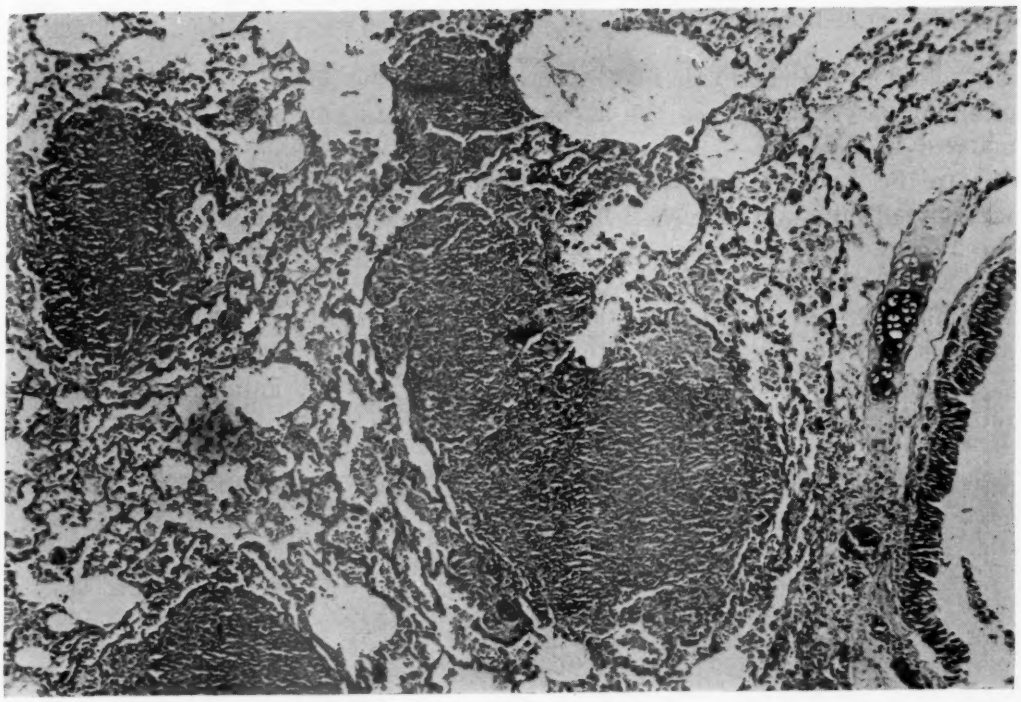


Fig. 10.—Photomicrograph (×87) of lung with end-to-side anastomosis. The process is similar to that seen in Fig. 7*A*.

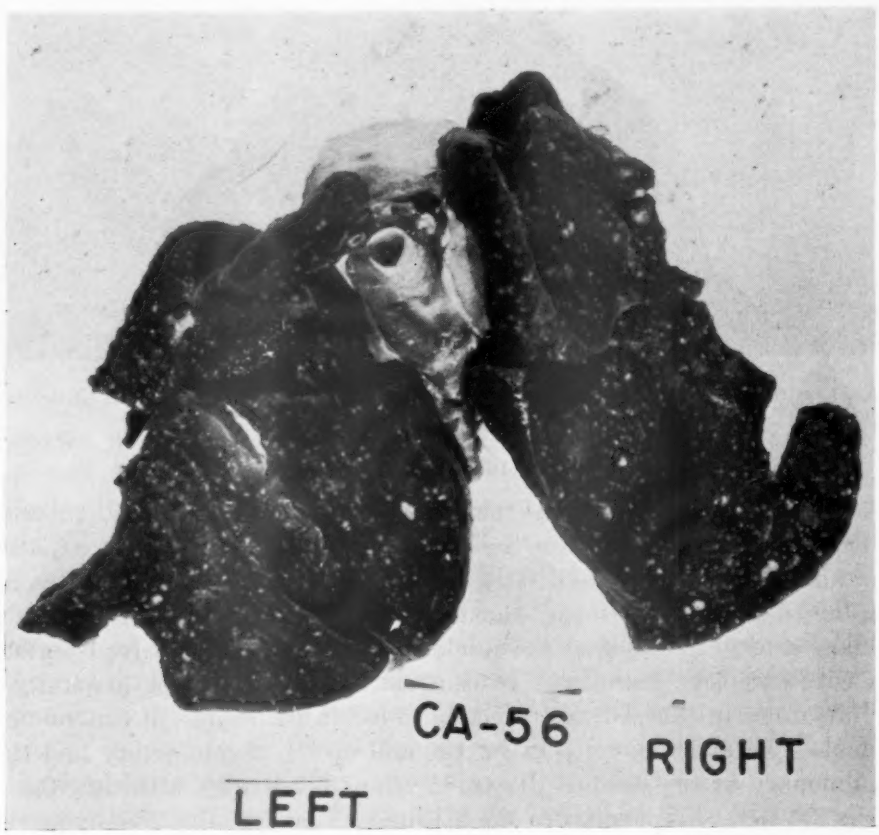


Fig. 11.—Control (no operation). Photograph showing equal distribution of fine miliary lesions in both lungs.

was found on the right side in 3 instances and on the left in 2. The distribution of pulmonary tubercles in the 22 monkeys not subjected to operation is summarized in Table II.

In the 2 control animals in which thoracotomy was performed there were widespread miliary tubercles in the lungs with no detectable difference between the 2 sides. Fig. 12 illustrates the lungs in 1 of these monkeys.

Extrapulmonary lesions in the 24 control animals were similar in character and distribution to those in the monkeys with the arterial shunts. Three animals in the control group had a few small lesions in the brain and meninges.

Microscopic studies of the lesions in the control animals demonstrated numerous tubercle bacilli and confirmed the gross autopsy findings.

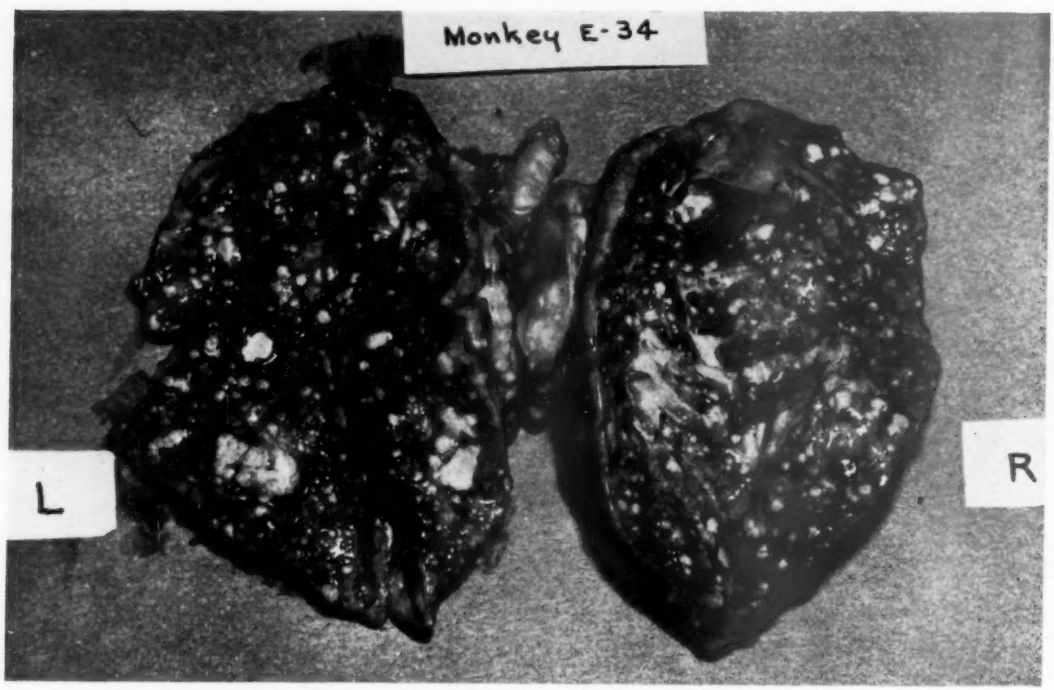


Fig. 12.—Control thoracotomy, right. Photograph of lungs showing equal distribution of lesions on the operated and unoperated sides.

DISCUSSION

These experiments indicate that in monkeys with induced tuberculosis, diversion of systemic blood into the pulmonary arteries produces a pathologic process which differs from the disease in control animals. When this diversion is accomplished by an end-to-end anastomosis between a systemic artery and a pulmonary artery, the lung on the side of operation shows massive conglomerate lesions with extensive caseation. In contrast, the opposite lung generally shows the miliary form of tuberculosis typically found in both lungs of control animals. In animals with anastomosis between the end of a systemic artery and the side of a pulmonary artery caseous disease develops bilaterally, although the distribution is not necessarily equal in the 2 lungs. These results are summarized in Table III.

TABLE II. DISTRIBUTION OF PULMONARY TUBERCULOSIS IN 22 CONTROL MONKEYS (NO OPERATION)

DISTRIBUTION	NUMBER OF MONKEYS
More extensive on right	3
More extensive on left	2
Equal in two lungs	17

The factor responsible for these qualitative and quantitative changes in the tuberculous process is not immediately apparent. There are a number of variables which may result from an arterial shunt of the type used in these experiments.

In an end-to-end anastomosis between a systemic and pulmonary artery the oxygen content of the blood perfusing the lung on the side of operation is increased. On the opposite side the oxygen content of the blood perfusing the lung is unchanged, although the blood flow through this lung is increased since it now represents the entire output of the right ventricle. The relative amounts of blood flowing through the 2 lungs under the conditions of this type of anastomosis are unknown.

TABLE III. DISTRIBUTION OF PULMONARY TUBERCULOSIS IN 14 MONKEYS SUBMITTED TO OPERATION

NUMBER OF MONKEYS	OPERATIVE PROCEDURE	DISTRIBUTION OF DISEASE		
		MORE EXTENSIVE IN LUNG ON SIDE OF OPERATION	MORE EXTENSIVE IN OPPOSITE LUNG	EQUAL IN THE TWO LUNGS
9	End-to-end anastomosis	8	0	1
3	End-to-side anastomosis	2	0	1
2	Control thoracotomy	0	0	2

In an end-to-side anastomosis between a systemic and a pulmonary artery there is presumably an increase in blood flow and in oxygen content of the blood perfusing the 2 lungs. The degree of this increase and its partition between the lungs is uncertain.

Another factor which might possibly be altered by an end-to-end or an end-to-side anastomosis between a systemic and a pulmonary artery is the pulmonary arterial pressure.

Measurements of pulmonary arterial pressure by other investigators[15] have demonstrated no increase in tension under conditions similar to those in these anastomoses.

Finally, it is possible that the differences in the tuberculous lesions in the 2 lungs may result from changes in the usual hematogenous dissemination of tubercle bacilli. All of these animals were given the initial intravenous dose of tubercle bacilli before operation so that both lungs presumably received an equal number of infecting organisms. In contrast, after an end-to-end anastomosis there is probably an unequal exposure of the 2 lungs to the hematogenous dissemination of bacilli which occurs after the disease has become established. There would appear to be less likelihood of inequality of exposure of the 2 lungs to blood-borne bacilli after an end-to-side anastomosis.

It is apparent that investigation of the factors which have been enumerated must be carried out in an attempt to elucidate the pathogenesis of the changes

in pulmonary tuberculosis observed in these experiments. Experiments are in progress involving ligation of pulmonary arteries, production of pulmonary venous congestion, and alterations in environmental oxygen, together with variations in method and time of infection.

SUMMARY

We have studied the effects of altering the pulmonary circulation by anastomosis between systemic and pulmonary arteries in monkeys infected intravenously with human tubercle bacilli. Thirty-six animals were used in this study.

The anastomosis between systemic and pulmonary arteries was of the end-to-end type in 9 monkeys and of the end-to-side type in 3 monkeys. Twenty-four monkeys served as controls for the distribution of pulmonary lesions. Thoracotomy was performed in 2 of these control animals. In all monkeys the disease progressed to a fatal termination in 76 to 262 days.

In general, the monkeys with anastomosis showed an extensive caseous form of tuberculosis in the lung on the side of the anastomosis. In contrast, the opposite lung showed fine miliary lesions similar to those found in both lungs of control animals.

The factors which may be responsible for these changes in the character and distribution of the tuberculous lesions are briefly discussed.

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DISCUSSION

DR. C. R. HANLON (Closing).—I should like to add that in the end-to-side anastomosis it is difficult from the few cases we have done to state on which side the disease process may be expected to be more prominent. In our three cases, two have shown greater disease on the side of the anastomosis. Although theoretically in end-to-side anastomosis there is an equal distribution of the oxygenated blood to the two lungs, in practice, because of mechanical factors, it may well be that more oxygenated blood will be directed to the lung on the side of the anastomosis. This is suggested by the results shown here.

CARDIOTOMY INTO AN EMPTY LEFT VENTRICLE

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AN EFFICIENT and practical apparatus which would assume the function of the heart and permit diversion of blood from its chambers would undoubtedly extend the scope of cardiac surgery. Many significant contributions to the development of such a mechanical heart have been made by Gibbon,[1] Dennis,[2] Clark,[3] Bjork,[4] Jongbloed[5] and their co-workers. These investigators have been engaged in constructing an artificial oxygenating apparatus to be used in conjunction with their heart pumps. In contrast to this principle, Sewell and Glenn[6] have recently reported a method of shunting the blood around the right heart via a mechanical pump into the pulmonary artery, thereby utilizing the animal's own lungs. We have been interested in developing a special cardiac cannula which, when introduced into the left atrium, shunts all of the oxygenated blood returning from the animal's own lungs to a mechanical pump which then returns it to the systemic circulation. Such a simplified apparatus would overcome the difficulties of mechanical oxygenators, yet permit cardiotomy into an empty left ventricle.

It was necessary to employ a mechanical pump which would adequately maintain circulation without being injurious to the elements of the blood, and to devise a means of collecting the oxygenated blood as it returns from the lungs, and of reintroducing it to the systemic circulation.

The method of utilizing an extracorporeal heart pump and the animal's own lungs instead of a mechanical oxygenator is schematized in Fig. 1. The venous blood is in black, the oxygenated blood is gray, and the left ventricle is shown empty. The left atrium is chosen as the site from which to collect the oxygenated blood. In order to accomplish this, a specially devised double-purpose cannula (to be described later) is introduced through the left auricular appendage into the left atrium. The oxygenated blood, returning from the animal's own lungs, is prevented from passing through the mitral valve into the left ventricle by means of a mechanical diaphragm placed across the entrance to the valve. The blood is then drawn into the cannula and carried off to the pump. It is then returned to the aortic arch by means of a glass cannula inserted in the proximal segment of the divided left subclavian artery. The blood, having re-entered the aortic arch, is now free to flow in all directions. In this manner, the entire systemic circulation is maintained, including that to the brain and the coronary vessels. This apparatus succeeds in completely diverting the flow of blood around the left ventricle.

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Read at the meeting of the Society of University Surgeons, Philadelphia, Pa., Feb. 9-11, 1950.

*U. S. Public Health Research Fellow in Surgery.

DETAILS OF THE APPARATUS

The Pump.—The pump (Fig. 2), a modification of the Dale-Schuster apparatus,[7] consists of a glass chamber, seated in rubber and mounted between metal plates. Contained within one end of the glass chamber is a rubber finger cot, the lumen of which is connected by a hose to a motor-driven air piston. When the air piston is in operation, the cot expands and contracts within the rigid chamber (in reciprocation with the action of the piston), producing a pulse

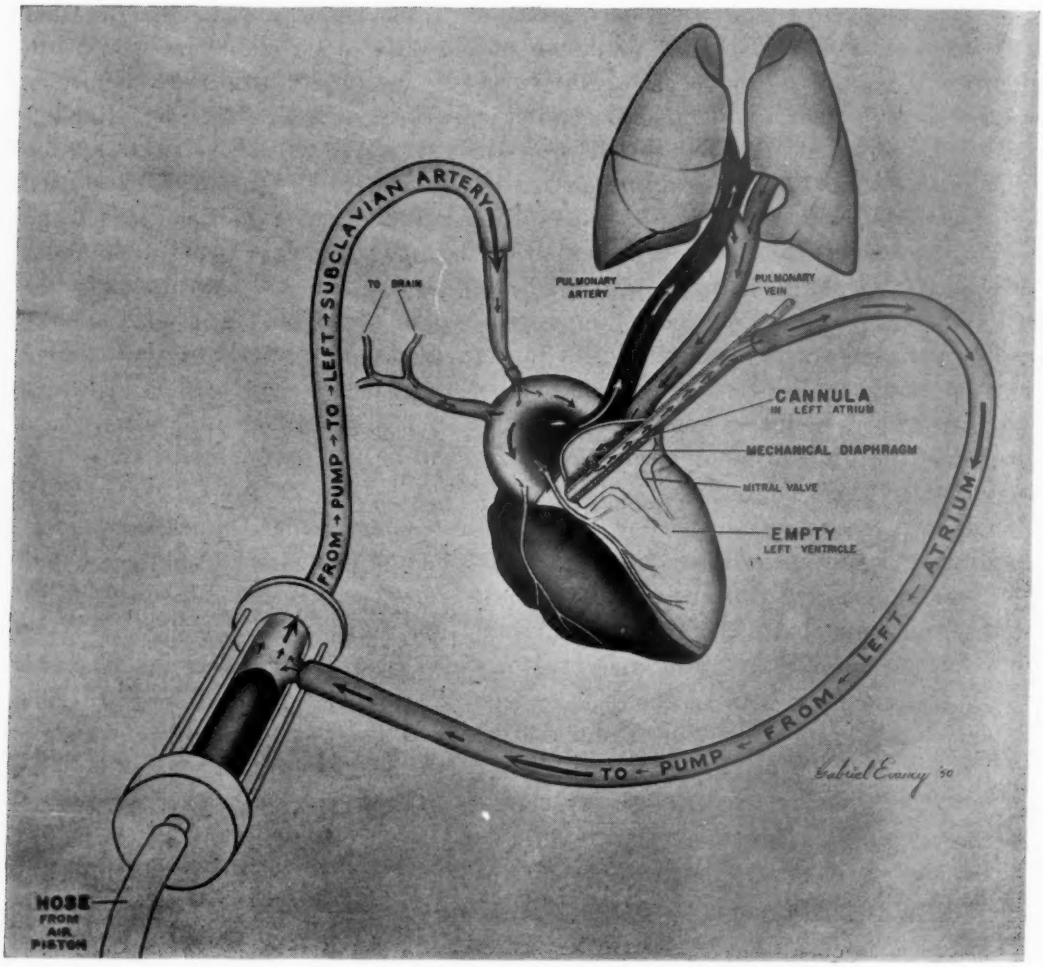
FROM → PUMP → TO → LEFT → SUBCLAVIAN ARTERY
TO BRAIN
PULMONARY ARTERY
PULMONARY VEIN
CANNULA IN LEFT ATRIUM
MECHANICAL DIAPHRAGM
MITRAL VALVE
EMPTY LEFT VENTRICLE
TO ← PUMP ← FROM ← LEFT ← ATRIUM
HOSE FROM AIR PISTON

Fig. 1.—Schematic view of the method by which the special cardiac cannula, positioned within the left atrium, shunts the oxygenated blood returning from the animal's own lungs to the mechanical pump. The blood is then returned to the systemic circulation via a glass cannula in the proximal segment of the left subclavian artery.

wave. Rubber flutter valves,* placed appropriately within the inlet and outlet tubing, direct the flow of blood. When the pump is in diastole (Fig. 2, *A*), with the cot contracting, the inlet valve opens, allowing the blood to flow into the glass chamber. In this phase, the outlet valve is closed. When the pump is in systole (Fig. 2, *B*), with the cot expanding, the valve at the outlet opens, permitting the

*Made by American Anode, Inc., Akron, Ohio.

egress of blood. At this moment, the walls of the inlet valve are collapsed, preventing backflow. The rate and volume of the pump are adjusted to meet the requirements of the animal's circulation by the simple expedient of observing the degree of filling of the left atrium. If the left atrium becomes distended, the pump is accelerated; if it tends to collapse, the rate is decreased. The amount of citrated blood required to fill this apparatus approximates 200 c.c.

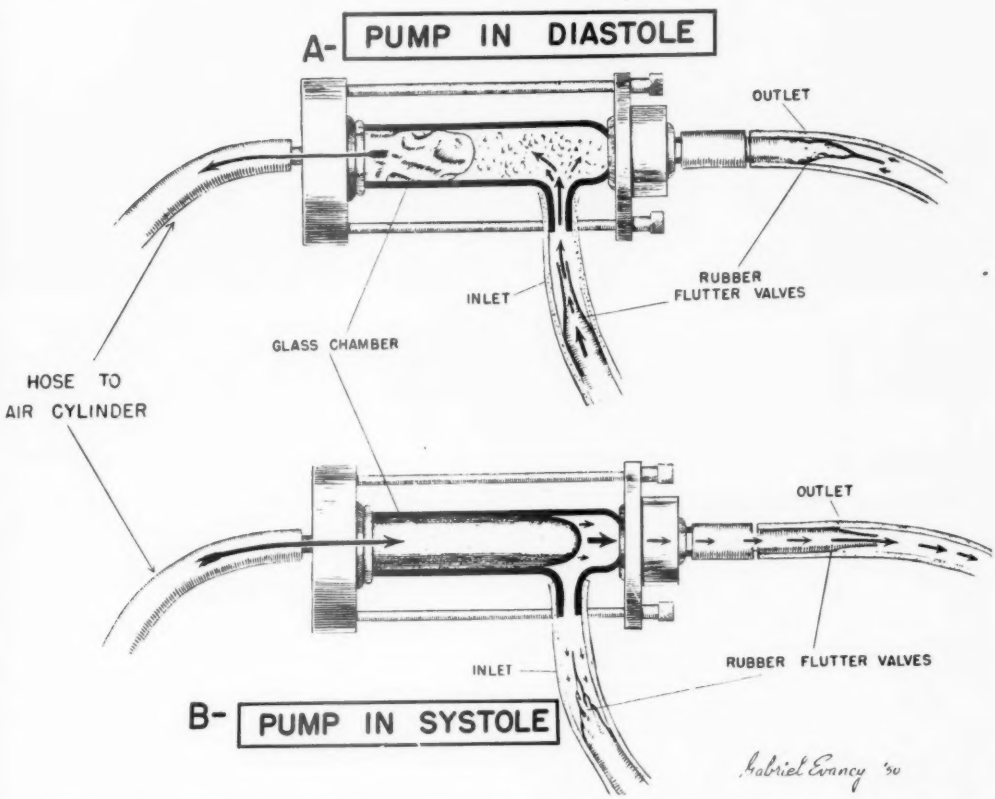

Fig. 2.—Drawing of the pump showing the flow of blood being directed by the action of the flutter valves, in both phases: *A*, diastole; *B*, systole.

The Cannula.—In order to assure complete collection of the oxygenated blood entering the left atrium, a special cannula was devised which was capable of performing a double function (Fig. 3). This cannula was designed, first, to prevent the oxygenated atrial blood from following its normal course through the mitral valve into the left ventricle, and second, to conduct to the pump that quantity of blood which normally enters the left atrium. Therefore, this cannula had two components: a partitioning mechanism and a hollow tube to convey blood. This was accomplished as follows:

The atrial cannula consists of a hollow metal tube with four movable metal leaflets mounted in the end which is introduced into the heart. On the opposite side of this same end there is a blood inlet which can be opened or closed. By turning a knob at the other end, the leaflets can be closed so that they fit into the contour of the tube (Fig. 3, *A*), or opened to form a circle (Fig. 3, *B*). A

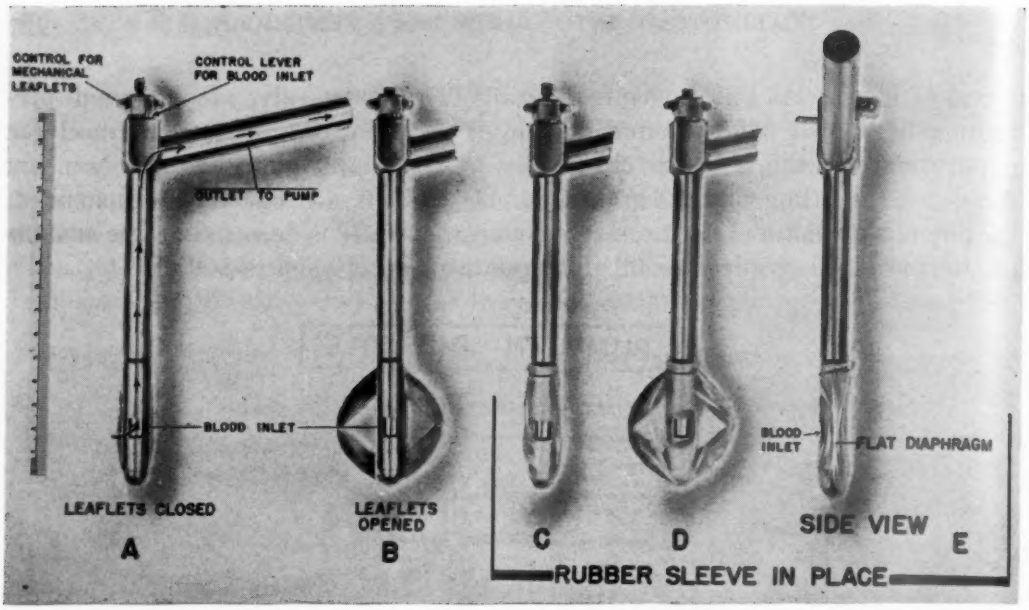

Fig. 3.—Photographs of the special cardiac cannula showing the blood inlet and: *A*, the leaflets folded; *B*, the leaflets opened; *C*, the rubber sleeve in place over the cardiac end and sealed to the edges of the blood inlet (the rubber over the inlet hole has been cut away); *D*, the same view as *C* showing flat diaphragm formed by the leaflets opening within the rubber sleeve; and *E*, side view showing the diaphragm on one side and the blood inlet on the other.

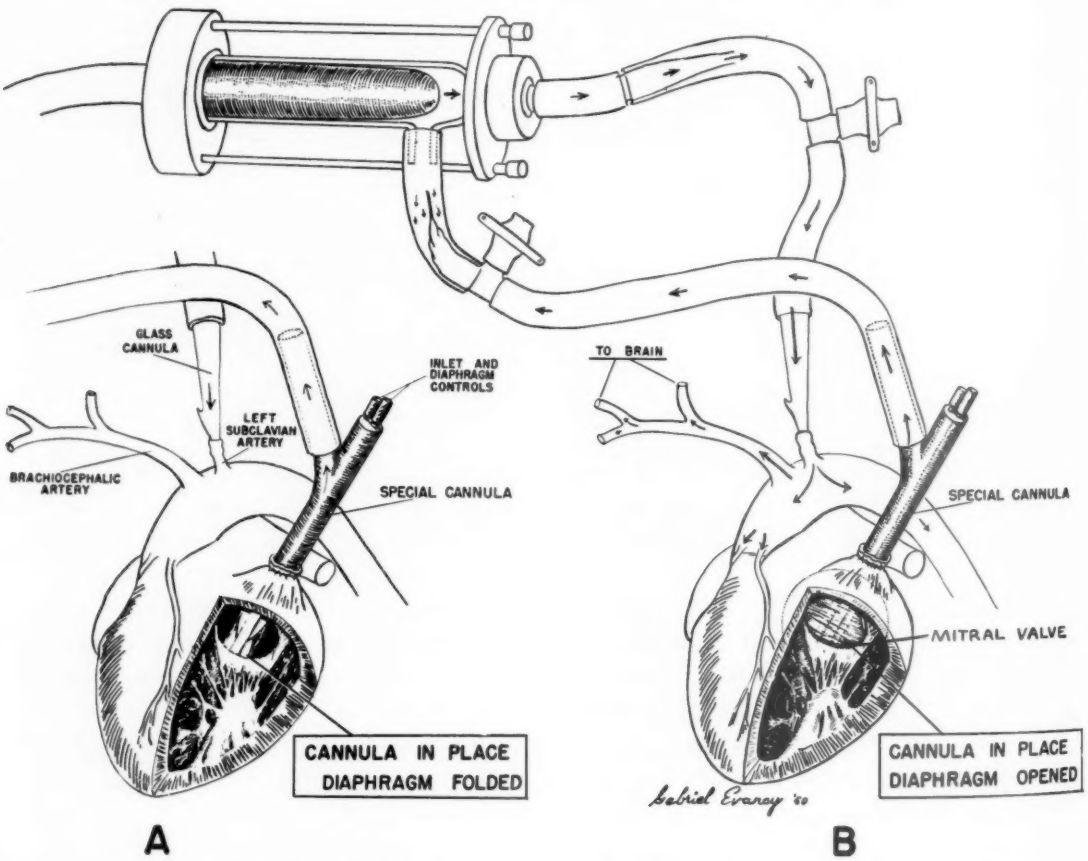

Fig. 4.—*A*, Drawing of the cannula lying within the left atrium, diaphragm folded; *B*, diaphragm expanded within the atrium, blocking the entrance to the mitral valve. The blood inlet is out of view on the other side, facing the orifices of the pulmonary veins in order to receive their oxygenated blood.

thin rubber sleeve is now pulled over this end and fastened to the shaft by means of an encircling ligature (Fig. 3, *C*). The rubber sleeve* is sealed to the edges of the blood inlet with latex and that bit of rubber which overlies the hole is cut out. When the leaflets are opened (Fig. 3, *D*), there is a complete, flat diaphragm formed by the action of the metal leaflets opening within the rubber sleeve. Fig. 3, *E*, a side view, demonstrates the relationship of the two components: the diaphragm on one side and the blood inlet on the other.

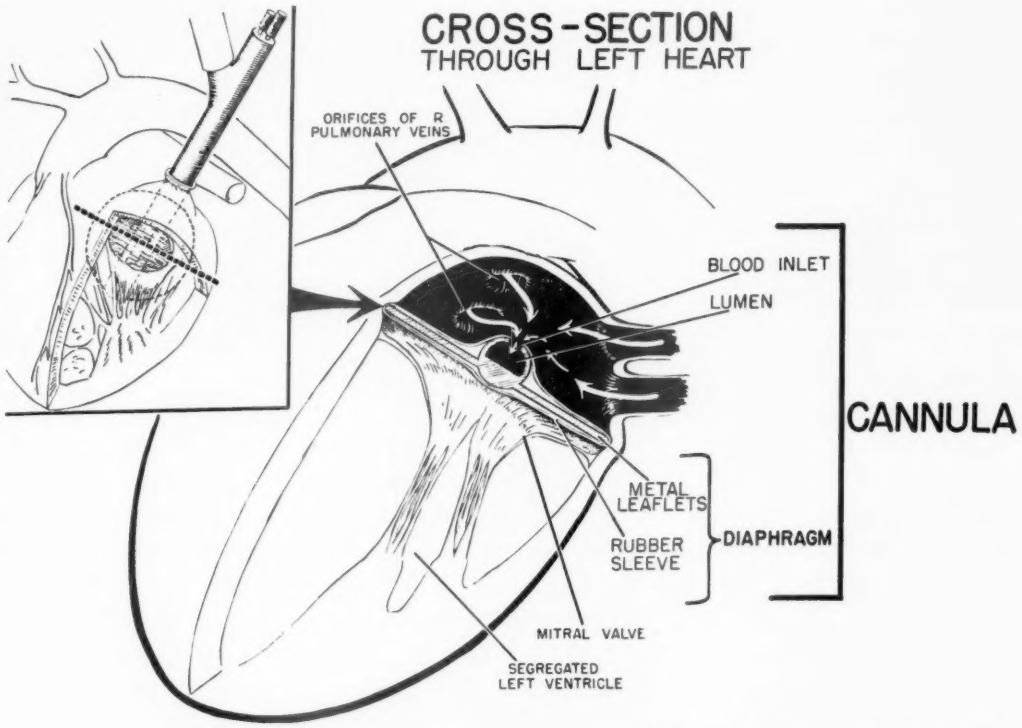

Fig. 5.—Cross-sectional view of the cannula in position in the left atrium with diaphragm expanded, showing partitioning action of the diaphragm interposed between the orifices of the pulmonary veins and the mitral valve. The blood is seen entering the lumen of the cannula instead of flowing into the ventricle.

The diameter of the cannula is 10 mm. The mechanism of the diaphragm is contained within a 4 mm. space, thus assuring ample lumen for the flow of blood which passes out the arm of the cannula.

By turning the respective controls, the diaphragm is folded and the blood inlet is closed. The cannula is inserted through the left auricular appendage into the atrium. Fig. 4, *A* illustrates the cannula lying within that chamber before the diaphragm is opened. The cannula is so positioned that the blood inlet (being on the other side out of view in these two drawings) faces the orifices of the pulmonary veins in order to receive their oxygenated blood. When the diaphragm is opened (Fig. 4, *B*), it lies within the atrium in a position to block the entrance to the mitral valve. Hence, on the one side of this cannula the surface of the open diaphragm faces the cavity of the left ventricle, while on the other side the blood inlet faces the orifices of the pulmonary veins. By this

*Made by American Anode, Inc., Akron, Ohio.

means, the oxygenated blood, being prevented from flowing through the mitral valve into the ventricle, passes into the blood inlet of the cannula instead. Fig. 5, a cross-sectional view, further illustrates the double function of the atrial cannula. The thin diaphragm, interposed between the pulmonary orifices and the mitral valve, arrests the flow of blood at that point, compelling it to enter the cannula.

DESCRIPTION OF THE OPERATION

All of the animals were premedicated with atropine sulfate, gr. $\frac{1}{100}$, and induced with sodium pentothal. Ether-oxygen was the main agent administered through an intratracheal tube. The chest was shaved, prepared, and the animal draped for a sterile operation. Air was displaced from the tubing and pump by stored, citrated dog blood. The mongrels used for this work were from 2 to 5 years of age and weighed 16 to 18 kg.

The chest was entered after resection of the left fifth and sixth ribs. As soon as the chest was opened, 100 mg. of procaine hydrochloride and 2 c.c. of 0.5 per cent cocaine solution were instilled through a small opening into the pericardial sac. The lung was then retracted downward and the left subclavian artery dissected from its bed. The vessel was ligated just proximal to its bifurcation into the left vertebral and axillary arteries. A curved vascular clamp (Blalock[8]) was used to occlude the vessel just as it comes off the aorta. The artery was then transected just below the ligature, and the proximal segment held up with two nerve hooks applied to opposite sides of the lumen in order to facilitate insertion of a glass cannula (Fig. 6, inset). After the cannula was tied in place, it was filled with heparin-saline solution and connected to the outflow tubing of the pump. The occluding clamp was removed and any residual air was allowed to escape through appropriately placed air traps.

The lung was then retracted laterally and the pericardium picked up and the opening enlarged to about 6 cm. just anterior to the phrenic nerve. The tip of the left auricular appendage was grasped with a Collins lung clamp and two mattress sutures were placed back-to-back very superficially in the epicardium of the appendage about 2 cm. from its tip (Fig. 6). Another mattress suture was placed at its base for ligation of the appendage at the conclusion of the procedure. With the assistant controlling hemorrhage by gentle traction on one of the two sutures, causing the appendage to be pinched between the suture and his index finger, an incision was made in the lateral wall of the auricle. Care was taken to curve this incision upward at the ends to prevent retraction. The cannula was filled with citrated blood and its tip placed against the opening in the auricle, the mattress suture was relaxed, and the cannula dropped into the atrium. Tension was immediately applied to both mattress sutures, which were then tied. The cannula was connected to the inflow tubing of the pump, the blood inlet door was opened, and the pump turned on. Even though there was suction at the blood inlet, it was noted that the greatest amount of blood continued to follow its normal route into the left ventricle until the diaphragm was opened. Therefore, only a portion of the oxygenated blood was diverted

to the pump, permitting a gradual reintroduction of the nonoxygenated blood in the apparatus to the systemic circulation. After a few beats of the pump, the glass chamber became filled with oxygenated blood.

The cannula was carefully positioned so that the diaphragm, when opened, would lie in a plane parallel to the mitral valve. The circumflex branch of the left coronary artery, which is seen coursing parallel to the ring of the mitral

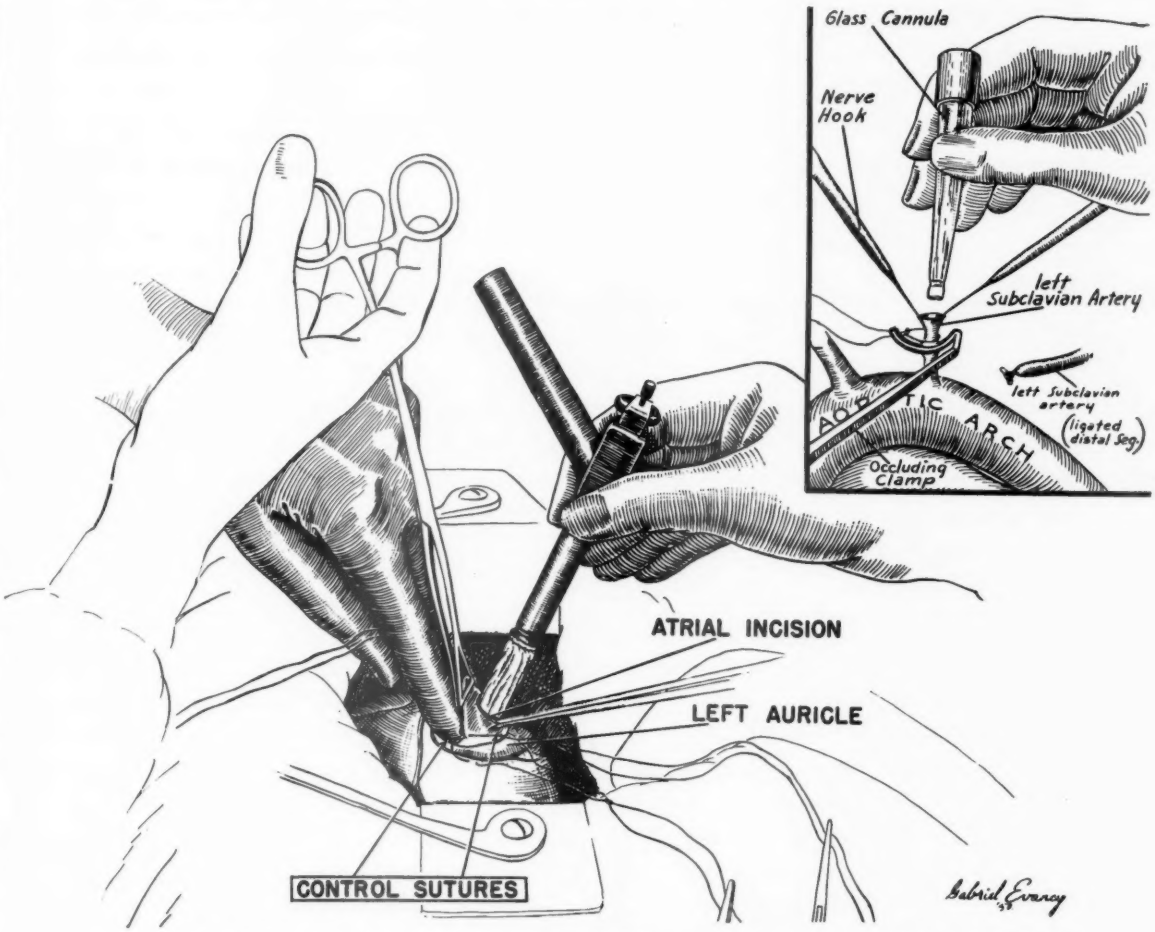

Fig. 6.—Drawing of the cardiac cannula, its diaphragm and blood inlet closed, being inserted into the left auricular appendage. The stay sutures and the method of controlling hemorrhage are demonstrated. The inset shows the glass cannula being inserted into the proximal segment of the left subclavian artery.

valve at the base of the appendage, was used as a guide. By turning the control knob, the diaphragm was opened. When this was done, all the oxygenated blood entering the atrium was shunted around the left ventricle by passing it through the cannula to the pump. An assistant held the cannula in position.

The left ventricle was then entered through a 2.5 cm. incision (placed between two rows of sutures) in order to confirm its exclusion from the systemic circulation. Instead of a gush of blood, only residual blood in the ventricular cavity plus oozing from the transected vessels in the myocardium was seen.

At the conclusion of the operation, blood oozing from the transected coronaries was allowed to enter the ventricle to prevent any air being trapped in that chamber. The ventricular wound was repaired with a layer of interrupted fine silk sutures. The appropriate controls on the atrial cannula were then manipulated in order to fold the diaphragm and close the blood inlet. After the left ventricle resumed normal rhythm, the pump was turned off. The cannulas were withdrawn and the auricular appendage and the left subclavian artery were ligated. Protamine sulfate was injected into a peripheral vein to neutralize the heparin.

The pericardium was partially closed to allow drainage, and the chest repaired in layers with interrupted silk. The animals were ambulatory and taking nourishment within twenty-four hours.

RESULTS

Dogs have been sustained by this apparatus for as long as twenty minutes with the ventricle open. However, the maximum length of time permitted with this apparatus has not yet been determined. It was interesting to note the behavior of the heart with the pump in operation: the left ventricle, perhaps because it was deprived of its work, became soft and contracted feebly, whereas the right ventricle continued to function normally. As soon as the blood load was returned to the left ventricle, it, too, resumed normal rhythm. Other than an occasional extrasystole, no arrhythmia ever occurred either during the insertion of the cannula or while the apparatus was performing.

The blood pressure in the carotid circulation was maintained around 120 mm. of mercury. Corneal reflexes and spontaneous respiratory effort were frequently noted to be present during the operation of the mechanical pump. Arterial oxygen saturation studies showed no appreciable reduction in saturation. Because mixed venous blood oxygen saturation determinations would indicate any tissue anoxia, blood samples were obtained by catheterization of the right atrium and were compared to prior samplings. There were only minor reductions. Electrocardiograms taken during the operation of the pump showed no significant electrical alterations, although the configurations do not lend themselves to interpretation at the present time.

Of the ten dogs submitted to this procedure, there have been five deaths. All of the deaths, except two, occurred at the operating table and were due to mechanical and technical failures attendant to the development of the method. Of the two exceptions one death occurred twenty-four hours postoperatively. In this instance, the lungs were accidentally excessively distended during surgery, resulting in prolonged anoxia with subsequent cardiac arrest. Heart action was restored by massage, but the animal suffered irreparable neurologic damage. The other death resulted from hemorrhage from a small tear in a subclavian vein accidentally incurred during surgery.

The survivors have not shown any undesirable sequelae, and some of them have been observed for as long as four months.

SUMMARY

1. An experimental method of shunting oxygenated blood around the left ventricle is presented. This method permits the use of the animal's own lungs for oxygenation of the blood.

2. Animals were sustained by this apparatus for as long as twenty minutes with the ventricle open in order to confirm the isolation of that chamber and the efficiency of the apparatus. The expected gush of blood was absent. Only residual blood in the chamber, plus oozing from transected vessels in the incision, was present.

3. The survivors have not shown any undesirable sequelae.

4. Further work seems warranted to exploit the opportunity offered by this experimental method for intracardiac surgery under direct vision and will be undertaken later.

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DISCUSSION

DR. C. DENNIS.—First I would like to congratulate the authors on this very ingenious device. I can assure you that I shall go home and try the same thing in our apparatus we are trying to develop in the laboratory. I would like to point out, though, that there is a consideration which Dr. Gibbon and I discussed at considerable length, at the time that Dr. Glenn and his associates presented the apparatus which they used for short-circuiting the right side of the heart as the present authors have short-circuited the left side, and that is this: Dr. Gibbon and I might be subject to considerable criticism because of the amount of time and effort and money we have employed to develop a machine that would short-circuit the entire heart if it could be proved that such an apparatus as that described today would do the job without.

It seems to us it is necessary to have not only a mechanical heart but also a mechanical oxygenating system, if one is to attack the majority of the cardiac problems which remain as forbidden territory to surgery at the present time.

Most of the difficulties which remain, it seems to us, are those in which the entire heart must be relatively quiet, both sides of the heart must be empty, and there must be

access not only to the ventricle but to the auricles on both sides of the heart during the surgical procedure.

To us, therefore, it seems that it is necessary to have not only pumps that would take care of both sides of the heart but also a mechanical oxygenator that will put the whole cardiorespiratory apparatus at rest.

Nevertheless it seems to me to be a very ingenious device and it may open up possibilities for our research purposes, with possible clinical applications that have been impossible previously.

DR. V. O. BJÖRK (Stockholm, Sweden).—I want to congratulate the originators of this very ingenious apparatus. I want to ask if you have a considerable amount of back bleeding or if you have any trouble with the apparatus staying there. Do you have to hold it with one hand during the time you open the left ventricle, or can you leave the apparatus? Does it happen that the apparatus might slip back so one of the pulmonary veins just comes out on the other side? Those are the only questions I have.

DR. H. D. SIRAK (Closing).—We have not tried this apparatus on any animal which has had an insufficiency of the aortic valve. We have not been troubled with any back bleeding. With regard to the cannula, it is held in position by an assistant. When the diaphragm expands, it stretches the wall of the atrium in the area of the mitral annulus, forming quite a secure fit.

OBSERVATIONS ON EXPERIMENTAL ATRIOVENOUS ANASTOMOSES, WITH PARTICULAR REFERENCE TO CONGENITAL ANOMALIES OF THE VENOUS RETURN TO THE HEART, AND TO CYANOSIS

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(From the Laboratory of Experimental Surgery and the Cardiovascular Laboratory, Stanford University School of Medicine)

A NEW technique may be applied to some practical operative end, and it may be used as an aid in physiologic investigation. Previous work in our laboratory has demonstrated the technical practicability of performing right atriocaval shunts in the experimental animal, and the suggestion was made that the method might have an application in the treatment of chronic superior vena caval obstruction.[1, 2] Furthermore, this study demonstrated that one could manipulate and suture certain portions of the right atrium without causing serious disturbances in cardiac function.

As the investigation progressed techniques were devised to anastomose large veins to the left atrium. A shunt of this type presented intriguing possibilities. The transfer of either the superior or inferior caval blood to the left atrium, it was thought, would produce a situation in which there is a mixing of venous and arterial blood, and a cyanotic animal. One might then use this method in a study of cyanosis, and also observe the physiologic changes which would result in time. The experiment is similar to that of Blalock's,[3] in which unsaturated blood was made to return to the left atrium by establishing a shunt between a pulmonary artery and vein, but differed in that in his experiment part or all of one lung was sacrificed, which introduced a pulmonary factor.

Clinically, such an atriovenous shunt, if proved to be reasonably safe and technically feasible, might be used in the surgical correction of certain anomalies of the venous return to the heart. There are a number of excellent pathologic and embryologic studies on this subject.[4-11] In our own clinic, Purdy and Parsons have recently reviewed the literature and described the findings in a typical case.[12]

A persistent left superior vena cava is one of the most common of the anomalies affecting both the systemic and the pulmonary venous return to the heart. This malformation in itself is compatible with a long and active life, but often there are associated venous abnormalities which place a burden on the heart. For example, not infrequently the caval anomaly is combined with abnormal pulmonary veins which empty into the right atrium directly, or into the right superior vena cava, or into a vein which connects with the right superior vena cava. When only a few pulmonary veins empty into the right atrium by these routes, evidently there is little physiologic disturbance. In

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some instances, however, all of the oxygenated blood from the lungs is conducted into the right atrium through aberrant pulmonary veins which connect with a persistent left superior vena cava, which in turn drains into the right superior vena cava through a communicating vein (Fig. 1). In such cases life depends upon the patency of the foramen ovale and the ability of the right chambers of the heart to withstand the increased work demanded of them. At best, this leads to chronic invalidism, and often is responsible for early death. A rare type of aberrant venous return is the emptying of the cavae into the left atrium. It is usually associated with other serious malformations of the heart which in themselves often are not compatible with life for more than a few months. Many of these congenital defects have been undiagnosed during life. Now, with the assistance of cardiac catheterization and angiocardiography, it is reasonable to expect more frequent and accurate diagnoses.

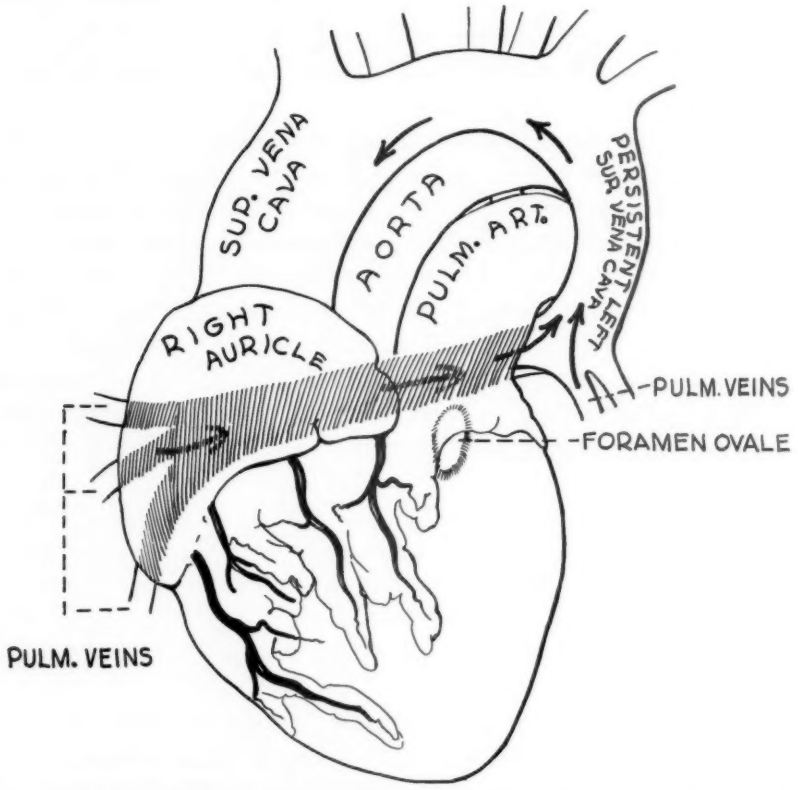


Fig. 1.—Persistent left superior vena cava with all of the venous return from the lungs emptying into the right atrium. Condition found at necropsy in a young woman who had right heart failure. To reach the systemic circulation blood must pass through a patent foramen ovale.

The correction of the anomaly in which all of the pulmonary venous return enters the right atrium would result in the sudden transfer of a large volume flow of blood from the right to the left chambers of the heart. It was impossible to duplicate this exact situation in the experimental animal. However, since the superior and inferior vena cavae normally empty into the right atrium, it was thought that the transfer of one or the other of these vessels to the left atrium

might, in a sense, simulate the shift. There are, of course, outstanding differences between the experimental situation and the anomaly. In the latter, a patent foramen ovale is present, and here the shunt would transfer work from the overburdened right side of the heart to an underdeveloped left side of the heart.

Although this study is in progress, and some aspects of it are as yet incomplete, it seemed proper to report the results attained. The complete data on the hematological changes which have occurred in response to the created cyanosis will form the subject of a separate communication. This seemed advisable, since we were anxious to keep a number of these animals under observation for a long period of time.

GENERAL PROCEDURE

The experiments were conducted on twenty-five adult dogs weighing 10 to 21 kg. Anesthesia was obtained with veterinary Nembutal. A mechanical respirator and endotracheal tube were used. In a few instances, oxygen was added to the air in the intratracheal tube, and most often it was continued during the postoperative period until the animal recovered from the anesthesia. The vascular suture was accomplished with number 00000 arterial silk on a No. 9 minimum trauma needle. In practically all instances the continuous everting suture with two interruptions was used. Approximately 1 c.c. of heparin solution was applied at the anastomotic site. Before closing the thorax, 100,000 units of penicillin were instilled into the pleural space. The ribs or sternum were approximated with linen sutures, and the various other layers with interrupted silk. Most of the animals received up to 250 c.c. of 5 per cent glucose in saline solution during and after the procedure. Patency of anastomoses was determined by angiograms or necropsy. The pre- and postoperative blood studies included a hematocrit, hemoglobin, oxygen capacity, oxygen content, and oxygen saturation. The samples were taken by direct arterial puncture in the unanesthetized animal.

LEFT ATRIO-SUPERIOR CAVAL SHUNTS

These experiments were conducted to determine whether it was technically feasible to shunt the superior vena cava into the left auricular appendage, and to observe the effects produced by such a shunt.

The operative approach for the left atrio-superior caval type of anastomosis was the median sternotomy, extending from the xiphisternum to the first rib. The pericardium was picked up, and 3 c.c. of 2 per cent procaine were injected into the pericardial sac and allowed to remain in contact with the heart for several minutes. The superior vena cava was freed of its investments from the insertion into the heart to the first tributary veins. The pericardium was incised longitudinally from the reflection at the superior vena cava to the diaphragmatic insertion. The left auricular appendage was grasped and held while a specially devised clamp was applied to its base. The upper end of the auricular appendage was cut off, care being taken to create an opening slightly larger than the width of the cava. The superior vena cava was then occluded with either a Potts' ductus or a bulldog clamp, and another clamp was placed

across the insertion of the cava into the auricle, preserving the entrance of the azygos vein. The cava was cut close to the clamp on the cardiac end, leaving a small cuff protruding beyond the clamp for subsequent closure with a continuous arterial suture. The anastomosis was then accomplished with an everting suture of arterial silk (Fig. 2). On an average, the superior vena cava was

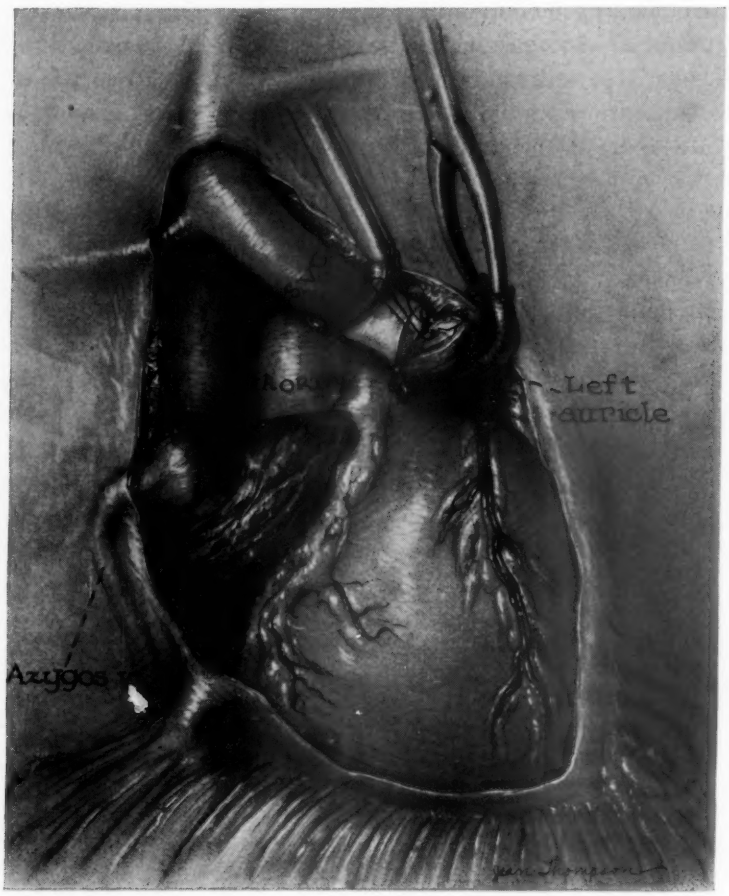


Fig. 2.—Technique of performing a superior vena cava-left auricle shunt. Various types of occluding clamps have been used. Perhaps the best is the one shown in Fig. 4.

occluded for twenty-five minutes and the animals showed no apparent ill effects therefrom. There was only one instance of serious disturbance in cardiac rhythm during the operations. In order to hold the heart toward the right side of the thorax, the open pericardium was sutured to the anterior thoracic wall, in the midline, thus forming a new anterior mediastinum.

There were twelve animals in this group, eleven of which survived the operation. One died during the procedure from ventricular fibrillation, and this animal was noted to have an abnormally fast heart at the beginning of the experiment. Five animals died within the first three weeks, two from chylothorax, one from an anastomotic leak on the tenth day, and two unexplainably, one on the tenth and one on the seventeenth day. One animal died on the

thirtieth postoperative day from an overdose of Diodrast. In only two instances was there occlusion of the anastomosis, as demonstrated at necropsy or from angiograms. In general, the long-term survivors of this procedure are not seriously disturbed by the alteration in circulation and exhibit only a mild degree of cyanosis.

The average preoperative arterial oxygen saturation of this group of animals was found to be 92 per cent, and at various periods of time from one week to a number of months after the left atrio-superior caval shunt, the postoperative arterial oxygen saturation averaged 82 per cent.

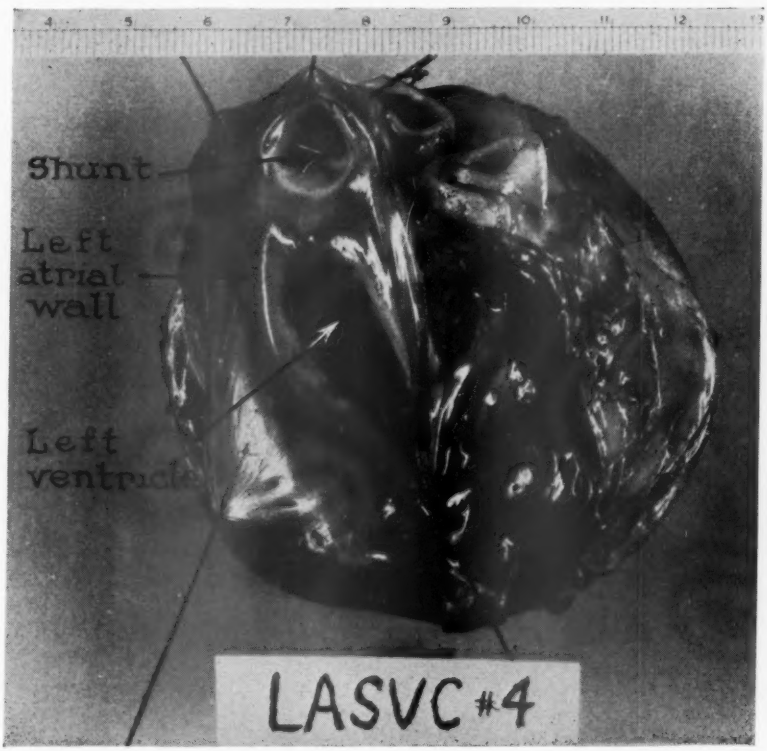


Fig. 3.—A left atrio-superior vena caval shunt of ten months' duration. The stoma permitted the passage of a No. 34 bougie.

Measurements of the anastomoses in the animals which died or were sacrificed averaged a No. 24 bougie, while the superior vena cava averaged a No. 34 bougie. In one animal which was sacrificed after ten months, there was practically no measurable difference between the anastomotic site and the superior vena cava, both accepting a No. 34 bougie. The union was smooth and soft, and the silk suture could be seen lying beneath the intima (Fig. 3).

LEFT ATRIO-INFERIOR CAVAL SHUNTS

These anastomoses were done to study the technical feasibility of anastomosing a large vein to the left atrium, to determine whether there would be any adverse effect when a large volume of blood was diverted into the left side of the heart, and to observe the heart action while the atrium was being partially

clamped and sutured. Furthermore, we were interested in knowing how much cyanosis would be produced by mixing all of the venous return of the inferior vena cava with the oxygenated blood in the left atrium.

The atrio-inferior vena caval shunts were accomplished through a left lower intercostal incision which exposed the lower portion of the heart and the diaphragm (Fig. 4). The pulmonary artery supplying the left lower lobe was isolated and a temporary ligature was applied to occlude it. The pericardium

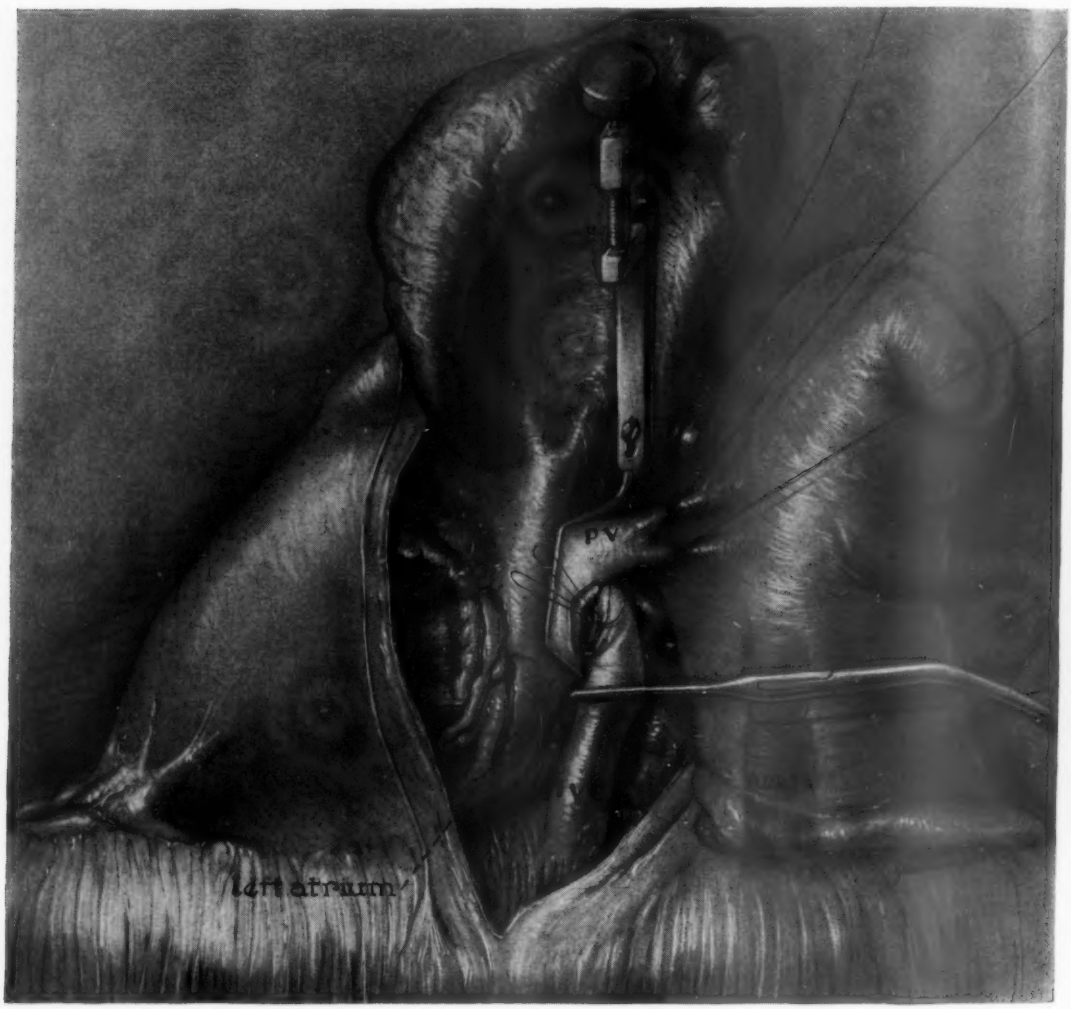
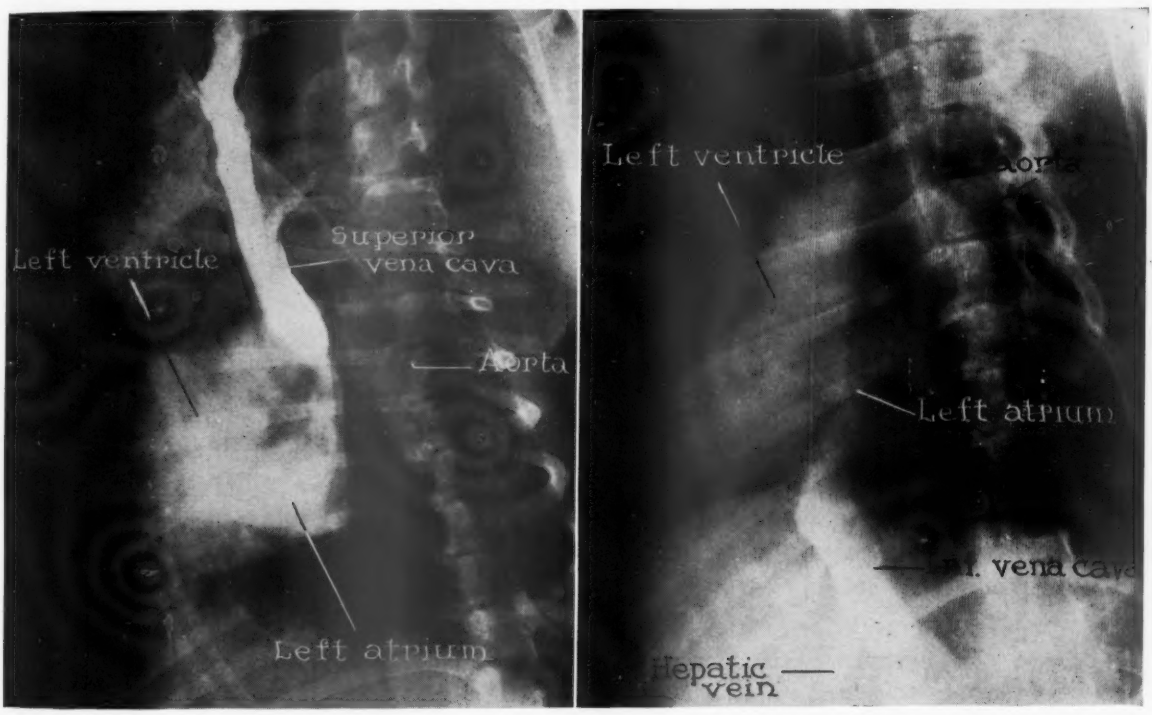


Fig. 4.—Technique of performing left atrio-inferior caval anastomosis. Best results were obtained if the aorta was almost completely occluded during the anastomosis.

was incised and dissected free from the pulmonary veins draining the left lower lobe. These were occluded with temporary ligatures. The inferior vena cava was next freed from the diaphragm to its entrance into the heart. A clamp was then applied to the left atrium, and an opening slightly larger than the diameter of the inferior vena cava was cut into the atrial chamber. The inferior vena cava was tied at its insertion into the right atrium, an occluding clamp was

applied about 3 c.c. distal to its insertion, and the cava was cut off close to the ligature. The atriocaval anastomosis was accomplished with a continuous everting suture of arterial silk. At the completion of the shunt, the clamp was first removed from the atrium to test the suture line; in a number of instances, an additional suture was required. The inferior vena cava was opened slowly so as not to throw too large a volume of blood into the left atrium at one time, and the ligatures on the aorta and pulmonary artery were removed a few moments later. As the flow of blood through the inferior vena cava was allowed to enter the left atrium, the heart rate usually decreased, and the atrium and the ventricle enlarged. Occasionally there were a few ectopic beats, but obvious cardiac irregularity was not observed. On an average, the inferior vena cava was occluded for twenty-five minutes during the procedure.



A. *B.*

Fig. 5.—*A*, Angiocardiogram of a left atrio-superior vena caval shunt of six months' duration, showing the dye entering the left atrium from the superior vena cava, passing into the left ventricle, and out the aorta.

B, Angiocardiogram of a left atrio-inferior vena caval shunt of three months' duration, showing the dye entering the left atrium, passing into the left ventricle, and out the aorta.

There were thirteen animals in this group. In the first seven no attempt was made to control the venous pooling in the lower extremities and viscera which occurred when the inferior vena cava was clamped. Only one animal of these seven survived the postoperative period and is living; all the others died in a state of profound shock within ten hours after the operation. The administration of intravenous infusions, vasoconstrictors, and intratracheal oxygen seemed to prolong the postoperative survival time, but they did not reverse the state of shock.

In the next six animals, during the time the inferior cava was occluded, the lower thoracic aorta was closed with a ligature to the point where only a small quantity of blood passed through and into the lower one-half of the body. Four of these six animals survived the operation and three are alive at the present time. One was sacrificed after one week because of an accidental burn. All four had diarrhea and vomiting postoperatively, which probably came as a consequence of the interference with the visceral blood supply during the operation. After several days of supportive feeding they began eating, and now, except for their state of anoxemia, they are getting along well. Angiographic studies confirm that all of the inferior vena caval blood passes through the left atrium, left ventricle, and aorta (Fig. 5).

Hematological and other studies on these animals will be reported in detail in a subsequent communication. Suffice it to say that this shunt has caused profound anoxemia. The average preoperative arterial oxygen saturation in the surviving animals was 92 per cent, and between two and twelve weeks postoperatively it averaged 70 per cent.

DISCUSSION

These experiments indicate that large veins can be anastomosed to the left atrium without causing serious disturbances in cardiac function during the operative procedure. Furthermore, they re-emphasize the fact that one can use accepted vascular suture methods on the atrium with good results, and that there is little danger of delayed hemorrhage from rupture of the suture line.

Of the thirteen animals which lived for ten to twenty-one days after the operations there were two with thrombotic occlusions of the anastomosis. Angiographic studies or necropsies on nine animals which have been observed for one to ten months revealed patency in each case. It is worth mentioning that a generous cuff of atrium was everted during the vascular suture so that no raw muscle protruded into the atrium, and a smooth intima-to-intima approximation resulted.

Transferring the venous return of the superior vena cava to the left atrium was tolerated quite well. On the other hand, shunting the inferior caval return was poorly tolerated unless the lower thoracic aorta was partially occluded during the anastomosis. All the latter group exhibited some degree of shock, however, and even those which survived had a difficult postoperative course. It was thought that most of this disturbance in physiology was due to venous pooling caused by temporary occlusion of the inferior vena cava, but the sudden creation of a state of low arterial oxygen saturation and the increased work for the left chambers of the heart, which occurred when the cava was opened, probably contributed as well.

This study substantiates the belief that the mixing of venous with arterial blood in the heart can be an important cause of cyanosis.[3, 13, 14] Mixing the venous return of the inferior vena cava with the oxygenated blood of the left chambers of the heart evidently reduces the arterial oxygen saturation about twice as much as when the superior vena caval blood is similarly shunted.

One of the purposes of this investigation was, if possible, to determine whether it would be feasible to correct certain anomalies of the venous return to the heart. It would seem from these studies that the technical aspects of such operative procedures might be practicable. Before embarking upon such a procedure one would have to be certain of the exact nature of the anomaly, as determined by angiography, cardiac catherization, and other studies. If it were determined that one was dealing with a malformation in which all of the venous return from the lungs emptied into the right atrium, and that was associated with a persistent left superior vena cava of large caliber and long enough beyond the cross connection with the opposite vena cava, one might be able to perform an atriocaval shunt without disturbing the venous return from the lungs during the anastomosis. A side-to-side anastomosis between the aberrant pulmonary veins and the left atrium is suggested by the proximity of these structures, and this might be possible by using a partial occluding clamp. The cross connection with the opposite vena cava could be ligated subsequently if either of these shunts were successful.

Perhaps if the aberrant left pulmonary veins alone were shunted into the left atrium this would relieve the right heart of enough of its burden. While doing such an anastomosis it would be necessary to temporarily occlude the left pulmonary artery. Atriovenous anastomoses using vessels as small as the individual pulmonary veins of the dog have proved to be unsatisfactory, due to subsequent closure with fibrosis.[2, 15]

CONCLUSIONS

1. Left atriovenous shunts are technically feasible if one has veins of large caliber to anastomose.

2. Large atriovenous shunts remain patent and functional in most instances if care is taken to evert a generous cuff of atrial wall.

3. Serious cardiac irregularity seldom occurs while the atrium is clamped, incised, and sutured. The use of 2 per cent procaine on the surface of the heart may be an aid in this respect.

4. After the superior vena cava was anastomosed to the left atrium the arterial oxygen saturation was reduced from a preoperative level of 92 per cent to an average of 82 per cent. Left atrio-inferior caval shunts reduced the arterial oxygen saturation to an average of 70 per cent.

5. Clinically, atriovenous shunts might be used to correct certain congenital anomalies of the venous return to the heart.

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DISCUSSION

DR. C. R. HANLON.—I have enjoyed this paper by Dr. Gerbode and his associates. We have been interested in this problem from both the clinical and the experimental standpoint.

In a number of dogs we have shifted the superior cava into the left side of the heart, but not in exactly the same way that has been described. That is to say, we have shifted the superior cava into the cardiac end of the superior pulmonary veins, dividing the superior pulmonary veins and doing an end-to-end anastomosis, which appears to us a satisfactory technique.

The oxygen saturation in these dogs generally drops to about 70 per cent and this figure has been maintained over periods of more than one year in some of our animals. Patency of anastomosis has been confirmed by angiocardiography both immediately after operation and after intervals of more than one year.

In shifting the inferior vena cava, our experience has paralleled that which has been described, which is to say that the animals tolerate it rather poorly. The number of immediate deaths has been reduced by more expeditious anastomosis and by partial occlusion of the aorta. We have anastomosed the inferior vena cava into the inferior pulmonary veins in the same fashion described for the superior cava, rather than into the auricle itself. We find that many of these animals die from the severe cyanosis.

In some cases, arterial oxygen saturation of 60 per cent is encountered, and values as low as 50 per cent have been obtained, probably because of superimposed pneumonia when the animal's condition began to deteriorate.

Our experience suggests that transfer of the inferior vena cava to the left side of the heart, if the anastomosis be widely patent, results in such severe cyanosis that it is scarcely tolerable, whereas shift of the superior vena cava is well tolerated and is, as Dr. Gerbode has said, an interesting way of studying cyanosis.

From the clinical standpoint, two patients with return of all the pulmonary veins to the right side of the heart have recently been operated on by Dr. Blalock. The preoperative studies in these cases have been reported by Dr. Richard Bing and his associates; one case had been extensively studied by Dr. Robert Ziegler of Detroit and will be separately reported.

As Dr. Gerbode has pointed out, the shift of the veins into the auricle with partial occlusion during the process might well be attempted and is certainly technically feasible.

THORACIC AORTIC COARCTATION

Its Experimental Production in Dogs, With Special Reference to Technical Methods Capable of Inducing Significant Intraluminal Stenosis

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INTRODUCTION

THE recent accomplishments in cardiovascular surgery have sharpened the interest of clinicians in this and allied fields. Among these, the surgical management of coarctation of the aorta has received considerable attention. In fact, data on the medical diagnosis and surgical technique have outstripped those complementary physiologic studies essential to a more complete understanding of this condition. This lag has resulted in part from a sparsity of cases available for thorough study as well as from awkward biological dissimilarities among random patients. The development of experimental preparations closely simulating this anomaly as it appears in man should resolve this disparity. This report details the methods used in developing animal preparations with a high grade of aortic coarctation at a point just distal to the left subclavian artery.

We have chosen the region of aortic arch close to the ligamentum arteriosum for the site of our study for several reasons: First, in man it is the site of obstruction in the "adult" type of coarctation of the aorta as initially described by Bonnet[1] and more recently accepted by Abbott,[2, 3] Reifenstein and associates,[4] and Bremer.[5] Second, it is the most difficult, readily available, site in which to produce obstruction. Third, the relative friability of the aortic arch contrasted with the toughness of the abdominal aorta,[6, 7] the magnitude of the normal expansile pulsation in this region of the aorta, and the proximity of this area to the heart make any method of successfully encroaching on the lumen of the vessel in this area safely applicable to a more peripheral artery. Fourth, the occlusion of the thoracic aorta in dogs is comparable with occlusion of the same area in human beings, whereas occlusion of the abdominal aorta of dogs is not comparable with similar occlusion in human beings.[8]

The whole problem of gradual obliteration of the thoracic aorta is inextricably intertwined with previous attempts to obstruct not only the abdominal aorta but such smaller ramifications as the femoral, popliteal, carotid, axillary, and brachial vessels. We believe that whereas the methods applicable to the thoracic aorta are applicable to smaller vessels, the converse is not true.

HISTORICAL

Before presenting our original investigations it appears advisable to review some of the previous reports, both experimental and clinical. The perti-

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nent literature rather handily falls into three separate spheres: (1) the mechanical problem of gradually occluding large vessels; (2) the hemodynamic and physiologic responses of an organism to partial aortic occlusion; and (3) the relation of the growth of the aorta to the growth of the animal as a whole.

The Gradual Occlusion of Large Arteries.—According to Matas,[9] the late eighteenth century first found physicians concerning themselves with the problem of slowly obstructing large arteries. In 1797, Deschamps[10] pointed out that gradual obliteration of popliteal vessels diminished the danger of gangrene following their division. Following his report there was a surge of interest in devising safe and simple methods of gradually obliterating the aorta for patients with aneurysms.

Because popliteal aneurysms were ostensibly cured by pressure appliances, Holmes,[11] in 1862, suggested using an abdominal pad and binder for gradually occluding aneurysms of the abdominal aorta. This method was first successfully applied by Murray of Newcastle-on-Tyne, in 1864, in a case of abdominal aortic aneurysm reported by him in 1871.[12] A somewhat similar device was described later by Gauss[13] (Fig. 1).

Unfortunately, lacerations to the abdominal viscera frequently resulted from the use of similar appliances designed for obliteration of the aorta by external compression. Milton[14] advocated using a rubber drain passing over the aorta with the two ends brought out around the lumbar spine to compress the aortic aneurysms against the vertebral bodies. Other surgeons[15, 16, 17] preferred either clamps or tourniquets of various types which had one attribute in common: they could be tightened gradually. All these methods presented two serious drawbacks: one, they regularly eroded the vessels to which they were applied, and two, they invariably resulted in an infected fistulous tract leading from the skin to the vessel wall.

In 1905, Halsted[18] first introduced an aseptic method for producing a gradual occlusion of the abdominal aorta in dogs. Whether he was guided primarily by an interest in vascular surgery or by his intense interest in the development of an aseptic technique for this as for other surgical procedures is not readily discernible. Certainly the role infection played in provoking erosion of vessel walls must have motivated strongly his attempts to provide a safer technique. His initial enthusiasm and successes[19] with ingeniously applied silver or aluminum bands were eventually dimmed by the development in each specimen of a progressive atrophy of the vessel wall beneath such bands. He concluded in 1913, that "Ultimately the metal bands must cut through the artery."[20] His subsequent interest was confined to wrapping vessels with such biologic substances as fascia lata, chromicized catgut, and homogenous aortic strips. In his experiments, as well as the subsequent studies by others,[21-24] the strips of fascia either stretched so much they proved ineffective or they cut through the vessel wall. No satisfactory instance of chronic aortic stenosis was produced.

In addition to the development of his aseptic compressive device Halsted made two other salient observations. He showed in the experimental animal

that stenosis in a large artery leads to poststenotic dilatation and that intima-to-intima approximation of an incompletely occluded vessel does not result in maintained cohesion or luminal obliteration of this area of the vessel wall. On the contrary, he noted that upon release of the constricting device the vessel returned to its initial size.

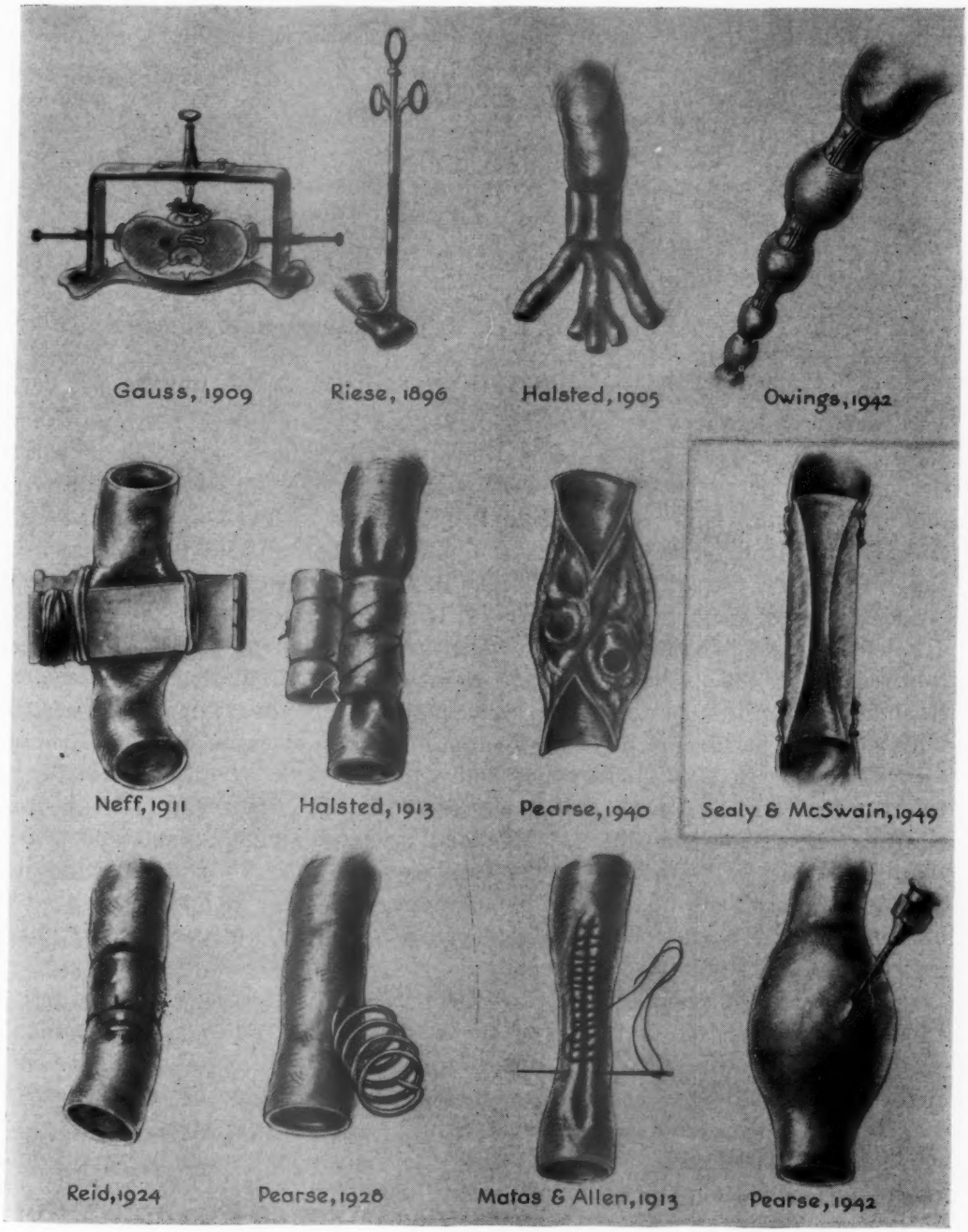


Fig. 1.—Earlier methods designed to occlude large vessels gradually.

In 1911, Matas[25] devised a somewhat simpler flat aluminum clip that was used clinically, in many instances with success, to occlude the carotid, femoral, and axillary vessels. Allen employed a similar band on the abdominal aorta in dogs and found that the aorta ruptured unless the original clamp was removed and replaced by a second proximal clamp within five to seven days.[26]

In 1911, Neff[27] introduced an unusual appliance consisting of a clamp wrapped with rubber bands. The jaws were separated by catgut or bone. When applied to the carotid arteries of dogs the intervening block of bone or the strands of catgut were removed by the action of the tissue enzymes and phagocytosis, therby allowing gradual approximation of the jaws of the clamp. However, in five dogs in which this device was applied to the abdominal aorta, erosion resulted in the three animals that did not succumb to peritonitis.

Recently, interest in extravascular compression has been renewed by Page[28] and Owings.[29] The former returned to a clamp of the Goldblatt type in his studies of "chronic constriction" of the thoracic aorta and found that all of his dogs died of rupture of the aorta in three to twelve days. Owings' work was first reported by Matas, in 1940, in a discussion of Pearse's comprehensive paper.[9] The original text did not appear until 1942; it outlined a laborious experimental study of seventy-nine animals on which 162 operations were performed over a period of three years. By the use of multiple broad rubber bands molded into a conical form fitting snugly around the aorta, Owings was able to constrict the aorta sufficiently over a period of months so that in four animals, it could ultimately be divided, at levels between the fifth and eighth intercostal spaces. The complications he experienced were hemorrhage following erosion in twenty-eight instances, and death due to overconstriction of the aorta in 18 animals. In the animals in which the aorta was divided, extensive collateralization was clearly demonstrated by Hill's[30] injection technique. These dogs gave no evidence of hepatic or renal insufficiency. Examination of the eye grounds revealed many changes commonly assoicated with severe hypertension in human beings. Subsequently, in the same laboratory, Blalock[31] gave up Owings' method of producing coarctation after forty-two attempts because of the frequency of secondary hemorrhage. In the one clinical trial reviewed by Matas, Monahan used the Owings' band and found that the aortic wall proximal to the band developed an aneurysmal dilatation with rupture and secondary fatal hemorrhage. Whether or not the pathologic condition of the aorta was directly responsible for this unfortunate complication was not definitely stated.

Reid[32] may be credited with the utilization of an intravascular obstruction to accomplish gradual occlusion of the aorta. He introduced intraluminally rolls of fascia to plug the aorta, thus producing an atresia, and suggested rolling the fascia about a small tube to provide for passage of blood distally. Pearse[8] tried small springs of steel, silver, and copper wire. These were threaded into the aorta at the level of the eighth interspace in twenty-four dogs. Of the twenty-one survivals, many had varying degrees of stenosis due to thrombosis in the area of the spring with subsequent recanalization. This provided an ingenious method, but was relatively uncontrollable and might lead

to unwanted emboli. His later attempts to produce a local thrombosis by exposure of a segment of the intima of the aorta to sodium morrhuate and 50 per cent glucose by intraluminal injection were uniformly unsuccessful.[9] More recently, Sealy and McSwain[33] reinvestigated the possibility of producing coarctation by means of intraluminal obstruction. They fastened into the aortic blood stream a polished Lucite tube, sufficiently doubly tapered to increase the peripheral resistance. Three dogs surviving up to five months continued to exhibit "arterial pulsations in the lower extremities."

Following the development of their aluminum clip, Matas and Allen added also a method of external plication of the thoracic aorta in dogs.[7] They used two- or three-staged procedures at three- to six-week intervals in 151 dogs. Each procedure was designed to produce 25 to 35 per cent occlusion over a segment one to three inches in length. Several animals with severe degrees of stenosis survived but no dogs lived after ligation of the aorta. They pointed out that failures were due to the absence of coalescence of the aortic wall as the sutures gradually relaxed and as the contralateral vessel wall bulged in response to the physical forces.

Subsequent to Matas and Allen's study of plication of the aortic wall little additional experimental surgery was carried out until 1924, when Reid[32] noted that all attempts to suture the vessel wall adjacent to an aneurysm were doomed to failure because of the frequent associated local pathologic conditions. Pearse,[9] however, attempted to constrict the vessel wall by injecting sodium morrhuate into the media, painting tincture of iodine or 25 per cent acriflavine on the wall, and applying a diathermy current with the hope of coagulating the vessel locally sufficiently to induce subsequent thrombosis. None of these methods resulted in a permanent constriction.

In 1939, Page[34] found that ordinary cellophane wrapped about a kidney led to the development of a heavy fibrous capsule which later constricted and produced hypertension in dogs, rabbits, and cats. Shortly therafter Pearse[9] produced a complete occlusion of the aorta by banding it loosely with similar material (DuPont No. 300 P.T. Cellophane). There followed such an intense perivascular reaction that he was loath to recommend its use in man. His own further attempts to reproduce these original results failed.[35]

Because of the considerable confusion and extremely erratic results obtained in various laboratories working with plastic films trying to produce or inhibit scar formation, a comprehensive survey by Ingraham, Alexander, and Matson[36] and a more selective study of the problem by Poppe and Renault de Oliveira[37] and Yeager and Cowley[38] resulted in at least a general understanding regarding which materials are effective fibroplastic stimulants and which are relatively inactive. Their conclusions were that Polythene DuPont 1.5 mil., type NV-7-14, stimulated a relatively standardized fibroplastic tissue reaction when prepared by the "stripping process" and adulterated with less than 1 per cent dicetyl phosphate. The dicetyl phosphate is a marked stimulant to fibroplasia. On the contrary, 300 PVT-71 DuPont Cellophane was found quite inert.

The enthusiasm for the use of such substances to reduce or maintain the caliber of vascular channels is partially supported by a growing list of clinical cases in which aneurysms have been wrapped beneficially. The actual diminution in the size of the vessel apparently depends upon the perivascular compression produced by the thickening of the adventitia and periadventitia.

Hemodynamic Considerations.—Several workers have demonstrated that a complete obstruction of the aorta immediately distal to the left subclavian artery is fatal for dogs if maintained for two or more hours.[39, 40, 41] Death in such instances was not ordinarily due to cardiac failure but rather due to pooling of the effective blood volume in dilated and engorged capillaries and veins distal to the site of the clamp. Additional light has been shed on this phase of the problem recently by Fine and co-workers[42] who observed that hemogenic shock was prevented by simultaneous perfusion of the hepatic artery with oxygenated blood at normal pressure. Whatever the mechanism, we have confirmed the observation that the aforementioned prolonged complete occlusion of the thoracic aorta uniformly results in death for every animal.

How much overload the cardiovascular system might tolerate has not been studied in either acute or chronic experiments. Instances of pulmonary edema in patients in whom the aorta had been tied off below the renal arteries have been reported, although, according to Reichert,[43] this procedure is well tolerated in healthy dogs. By inference we can assume that about 13 per cent of the blood might safely be forced into other channels, since Levy and Blalock[44] demonstrated that in the normal unanesthetized dog about 13 per cent of the blood leaving the left ventricle normally passed distal to the renal arteries. Fortunately, Mann and associates[45] studied the effect on the blood flow of luminal constriction of the carotid arteries. They noted that in a pressure system similar to that maintained by the heart muscle with a normally elastic arterial tree, a 50 per cent decrease in diameter is required to decrease the flow by 20 per cent provided the constriction is 8 to 10 mm. in length. For virtually all lengths the resistance to the flow would vary directly with the length of the constricted area.[46] Thus, for a 4 to 5 mm. constriction, one would require about a 60 per cent diminution in the diameter for it to be as effective.

Growth Factor.—The value of utilizing the growth increment was suggested and dealt with briefly by Holman and Beck.[47] The general relationship of the rate of growth of the cardiovascular system as compared with the rate of growth of the organism as a whole in the human fetus[49] and in infants and children[48] is available. However, precise measurements relating the rate of growth of the aorta to the organism as a whole are not available for dogs or for human beings.

THE EXPERIMENTS

Our experimental efforts to produce coarctation in the thoracic aorta were divided into two parts and will be discussed accordingly.

Part I:

1. Initial studies were made on the effects of incompletely compressive ligatures placed around the dog's aorta. Such ligatures were

made from bands of material believed to evoke a marked fibroplastic reaction when placed in contact with living tissue.

Part II:

1. To discover whether or not the interposition of a protective layer, such as homologous fascia lata, between an external compressive device and the wall of the aorta would protect the wall from atrophy and erosion.

2. To evaluate a readily reproducible method of narrowing the lumen of the aorta (hereafter referred to as "wedging" or "notching" of the aorta) with special attention to its advantages of controllability and absence of secondary erosion.

3. To measure in vivo the relationship of the diameter of the dog's aorta to the body weight.

4. To determine by biologic test the tolerance to initial obstruction of the canine aorta at the site of the ligamentum arteriosum.

5. To establish a colony of dogs with ascertainable coarctation, ranging from complete atresia to moderate stenosis. The creation of these preparations to serve in the further elaboration of the physiologic processes disturbed by this condition, which will be the subject of another publication.

Method; Part I

The first phase of this study has been carried out over a period of about two years. The knowledge gained from successes and from failures forms the basis for our subsequent progress in Part II. It is therefore worth considering the methods and results in detail.

We chose as our initial program the production in a single operative procedure of a constriction of 50 to 60 per cent of the diameter of the aorta over a distance of 0.5 to 1.0 cm. We felt that subsequent growth and constrictive fibroplasia would progressively diminish the remaining lumen.

Under aseptic precautions 150 animals ranging from 0.8 to 6 kg. were submitted to an exploratory thoracotomy through the third or fourth left intercostal space and the arch of the aorta was dissected free. This area of the aorta was then banded by three to ten layers of "cigarette cellophane" or with three layers of DuPont Polythene with less than 1 per cent dicetyl phosphate added. The films were sterilized by soaking twenty-four hours in 1:1000 aqueous Zephiran. Initially, the bands were simply tied down with a square knot (Fig. 2). Later, a single transfixing mattress type of suture of 0000 black silk was used to approximate the ends and to avoid the disadvantage of a large knot. In most cases no satisfactory positive pressure anesthesia machine was available. The operator relied solely on speed to enter and to close the chest as rapidly as possible in order to maintain a living animal. Frequently four to six such operations were performed in a single afternoon. At the completion of each procedure the chest was aspirated with a needle and syringe and the animal returned to its cage. No antibiotics, immunizations, or special feeding regimen was in force during this part of the work.

It is not surprising that the death rate from operative trauma, from initial over-occlusion of the aorta, and from infection was high. Disease, including particularly distemper, diarrhea, intussusception, and pneumonia, further reduced the colony. Erosion of the vessel wall by the bands was a frequent

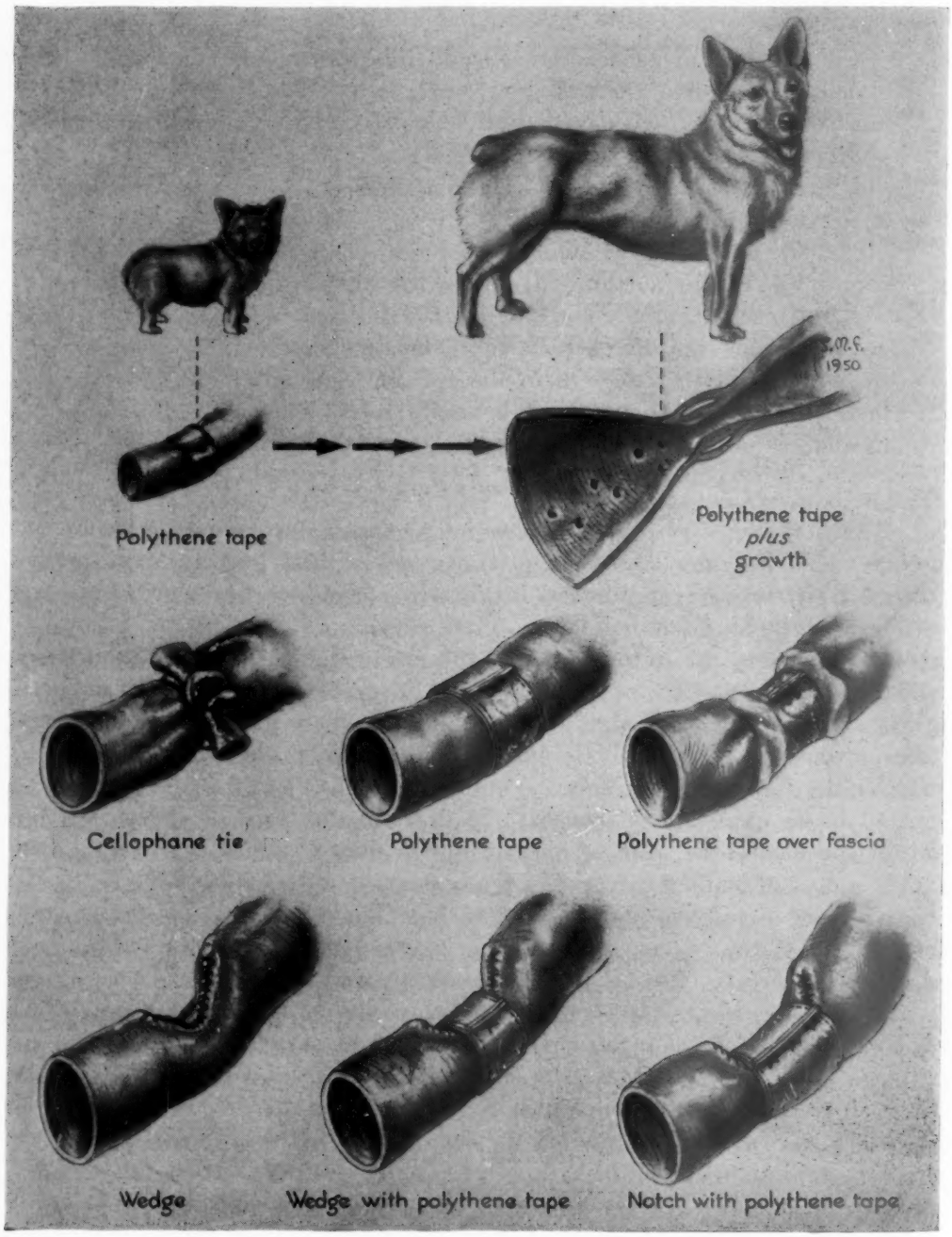


Fig. 2.—Methods of gradually occluding the thoracic aorta, used in the successful production of coarctation of the aorta in dogs.

occurrence. In consequence the net successes were reduced to ten adult dogs, of which three had coarctation of a severe degree and 7 of a moderate (Table I).

TABLE I. VASCULAR COMPRESSION PRODUCED BY A CELLOPHANE TIE OR POLYTHENE TAPE

Number of Dogs With Coarctation Produced		10
Moderate	7	
Severe	3	
Number of Unsatisfactory Results		140
Loss	5	
Disease	47	
Erosion	40	
Initial over-occlusion of aorta	15	
Heart failure	5	
Empyema	22	
Operation or anesthesia	6	
Total Number of Animals Studied		150

Method; Part II

Encouraged by the few successful experiments in which coarctation was produced, we set out to evolve a method with more predictable results. First, attention was directed toward reducing the losses from disease. Later it became increasingly apparent that most compressive devices encircling the thoracic aorta were destined to fail in a high percentage of cases for surgical reasons. We therefore improved our methods of surgical intervention and anesthesia, thereby allowing a wider range of experiments accompanied by a high survival rate.

Care of the Animals.—At the suggestion of a colleague* from the University of Minnesota School of Veterinary Medicine, increased protection was provided for the animal colony from those diseases that ravage puppies when they must live in kennels with adult dogs. Our accomplishments were somewhat hampered by existing physical facilities. However, the building of outside pens, on the rooftop, provided necessary spaces for expansion and furnished the growing animals with a more healthful environment, in addition to reducing the congestion of indoor quarters. Even during the severe winter weather of Minnesota, we were impressed by the general well-being of the dogs housed outside compared with that of those kept inside.

Feeding Regimen.—Regular feeding was of the utmost importance. All puppies under 6 months of age were fed two to three times daily from frequently sterilized pans. The average daily ration approximated 500 Gm. of horsemeat, 400 c.c. whole fresh pasteurized milk, and all the prepared dog biscuits each could devour.

Immunization.—To prevent distemper and interim infection, passive immunization was begun as soon as the pups were separated from the bitch, or at about 5 to 6 weeks of age. This consisted of a 5 c.c. canine homologous antidistemper serum† injected subcutaneously at three-week intervals. This was continued until the puppies reached 3 months of age, at which time active im-

*Dr. Clyde Beamis.

†Canine hyperimmune antidistemper serum, manufactured by Pitman-Moore Company, Division of Allied Laboratories, Indianapolis, Ind.

munization was begun, each puppy receiving a 5 c.c. ampule of canine distemper vaccine* at three-week intervals.

Disease.—Intestinal parasites were treated every three weeks with a vermifuge.† Any pup with diarrhea was isolated immediately and treated with parenteral streptomycin for three to seven days.

All animals developing distemper with cough and/or purulent nasal discharge were isolated and given 0.2 to 1.0 c.c. procaine penicillin in oil (300,000 units of penicillin per c.c.) intramuscularly every two days for the duration of the secondary infection. Occasionally streptomycin augmented this program with quite startling improvement.

Fluid therapy to the sickest animals did not seem to be of much value and in no instance did a severely dehydrated dog with diarrhea recover in spite of quite adequate parenteral hydration.

Three puppies developed intussusception and were operated upon; two recovered.

This routine, in addition to the care described, reduced the death rate due to disease from about 33⅓ per cent in Part I to about 10 per cent in Part II of this study.

Postoperative Infection.—The next problem dealt with was that of reducing the death rate from empyema. In addition to general measures of improvement in our aseptic technique, it was deemed advisable to institute a routine program of administering antibiotics postoperatively owing to the fact that in many instances a large foreign body, that is, wide Polythene tapes, remained in the chest. By giving 50,000 to 100,000 units of penicillin intrapleurally at the time of closure of the chest, and injecting three daily doses of 0.25 to 0.5 c.c. procaine penicillin in oil intramuscularly postoperatively, the death rate from wound infection and empyema declined from 15 per cent to less than 2 per cent.

Anesthesia.—A major improvement was made in the administration of the anesthetic. By modifying a Carmody-Israel ether-vapor and vacuum apparatus‡ it was possible to provide a controlled ether-air stream through a small endotracheal tube. With the use of the Meltzer-Auer principle of endotracheal insufflation[50] it was feasible to anesthetize safely puppies ranging in weight from 0.250 to 5.0 kg. When necessary, the surgeon could be his own anesthetist, since the use of this apparatus permitted the operator to control the ether concentration with sterile Allis clamps and to modify the endotracheal pressure by pressure of his foot on a run-off tube. The death rate from anesthesia in the Part II of this series was less than 2 per cent. At the completion of the procedure a two-holed No. 20 catheter was left in the chest, which was aspirated after the skin was closed. There were no deaths due to pneumothorax after the institution of this method for removing the residual intrapleural air.

The accumulated gains made possible from the techniques previously described were substantial. The deaths from intercurrent disease, anesthesia, surgery, and infection fell from over 50 per cent to less than 15 per cent.

*"Virogen" Bio. No. 666 manufactured by Pitman-Moore Company, Division of Allied Laboratories, Indianapolis, Ind.

†"Vermiplex" Nos. 1 and 2, manufactured by Pitman-Moore Company, Division of Allied Laboratories, Indianapolis, Ind.

‡Manufactured by V. Mueller & Co., Chicago, Ill.

During the period when we were modifying our methods to reduce our nonspecific mortality rates we were simultaneously modifying our approach to the problem of initial occlusion of the aorta.

Extravascular Fibroplasia (Fig. 2).—In an effort to produce a gradual occlusion of the thoracic aorta without involving any risk of erosion, the aortas of twenty-four puppies were loosely banded with an especially prepared tape (Fig. 3), three wraps of Polythene, "cigarette cellophane," tantalum mesh, or magnesium tape. These banding devices were carefully sutured in place with particular care taken not to allow any fixation suture to bowstring across the aortic wall and thus cut through. In addition, single, litter-mated animals had bands of cotton tape, heavy braided silk, and nonreactive Cellophane (DuPont 300 P.T.) similarly applied. These we used as controls for the series,

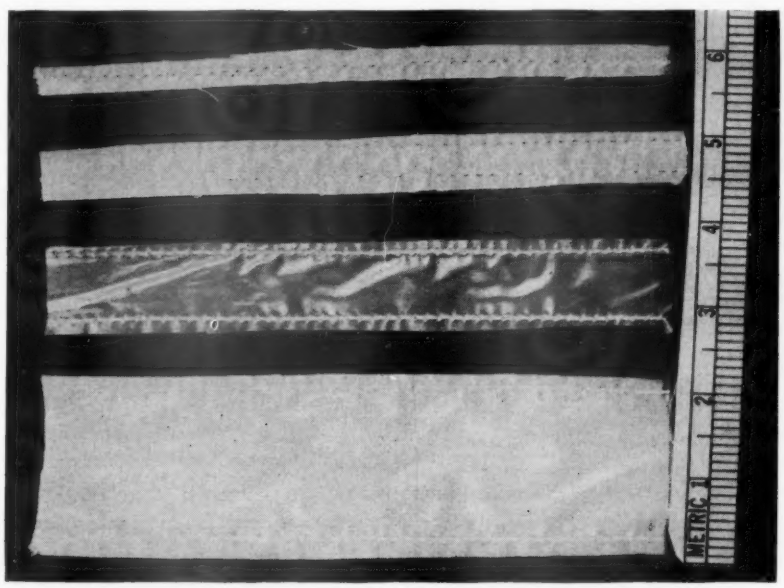


Fig. 3.—Tapes of various widths used in producing extravascular fibroplasia. Although varying in width, each is made up of six layers: three of reactive Polythene DuPont 1.5 mil., type NV-7-14; one of cotton cloth; and two of nonreactive Cellophane, DuPont 300 PVT-71.

and none have developed coarctation to date. On the contrary, thirteen banded with Polythene tape have already developed significant coarctation although their growth is not yet complete; ten have coarctation of a moderate degree and three have severe. The latter three dogs were all puppies banded on the second day of life when the aorta measured only 3 to 4 mm. in outside diameter. Since then they have grown in weight fifteen fold and their aortas have grown in diameter from 3 to 4 mm. to 10 to 12 mm. By virtue of growth alone they have attained luminal compression of 90 per cent and this exists over a distance of 0.5 cm. (Table II). The tantalum mesh and magnesium tape were uniformly unsuccessful.

Polythene Tape on Bands of Fascia (Fig. 2).—Initial success with the Polythene tape placed on top of a band of fascia encouraged us to continue the series with eighteen experiments. By using a 2 cm. wide strip of fascia lata, or rectus

TABLE II. EXTRAVASCULAR FIBROPLASIA PRODUCED BY POLYTHENE TAPE

Number of Dogs With Coarctation Produced		13
Moderate	10	
Severe	3	
Number of Unsatisfactory Results		11
Loss	0	
Disease	9	
Erosion	1	
Initial overocclusion of aorta	0	
Heart failure	0	
Empyema	0	
Operation or anesthesia	0	
Unaltered	1	
Total Number of Animals Studied		24

sheath, the aorta could be banded readily and constricted down to about 50 per cent of normal diameter. Over this was laid a 0.5 to 1 cm. Polythene band to support the fascia and provide for additional extravascular fibrosis. The incidence of erosion in this group was about the same as for those with a simple Polythene or cellophane tie, that is, about 25 per cent. This method had the disadvantage of making the estimation of the degree of occlusion very difficult since the aortic wall and the heavy fascial layer were necessarily interposed between the lumen and the band. Twenty per cent of the animals died of overocclusion of the aorta.

Of the surviving dogs there were four with a moderate degree of coarctation, two with a severe degree, and one with complete atresia (Table III). Examination of the perforated lesions showed that the bands cut through both the fascia and the aortic wall. In some instances after two to three weeks no remnant of fascia remained at all.

TABLE III. VASCULAR COMPRESSION PRODUCED BY POLYTHENE TAPE OVER FASCIAL BAND

Number of Dogs With Coarctation Produced		7
Moderate	4	
Severe	2	
Atretic	1	
Number of Unsatisfactory Results		11
Loss	0	
Disease	2	
Erosion	5	
Initial overocclusion of aorta	4	
Heart failure	0	
Empyema	0	
Operation or anesthesia	0	
Total Number of Animals Studied		18

Wedges and Notches (Fig. 2).—The third method employed is the soundest experimental approach to the problem of gradual occlusion of the aorta that we have found. It appears to be a logical and direct method for the occlusion of a large vessel, granted it is not so damaged by disease as to be unable to support safely a suture line.

This group of twenty-five animals ranged from 500 Gm. to 13 kg. and included four adult dogs. The aorta was freed up widely, the ligamentum arterio-

sum divided, and in some instances one pair of intercostals ligated to allow room for a clamp of the Pott's variety when it was used. If this clamp could not be readily placed without damaging more than one pair of intercostal vessels we found it was necessary to cross-clamp the aorta with serrefine or Gross type of aortic clamps. If the cross-clamping was continued for thirty minutes most of the animals developed some degree of spastic paralysis of the hind legs similar to that previously reported by Gross and Hufnagel,[51] Sako and associates,[52] and others.

To avoid this complication we used a small Polythene tube* measuring .062 inch in inside diameter for dogs up to 10 kg., or .085 inch inside diameter in larger animals, to shunt blood from the left subclavian artery to the aorta distal to the clamps.[53] This plastic prosthesis was treated internally with Silicone oil† to delay clotting. None of the animals in which this small shunt was employed subsequently developed either neurological or visceral changes, even though the aorta was purposely clamped as long as two hours in several experiments.

The operative procedure carried out on the aorta itself was relatively simple. The diameter of the aorta was measured with Vernier calipers. The aorta was clamped. The amount of aorta to be incised or excised in order to produce the desired initial increase in resistance was calculated. The desired portion of the aorta was measured off and two mattress sutures placed as markers. The incision in the aorta to produce a wedge, or excision of a segment to produce a notch, was carried out as precisely as possible. The adjacent edges of the vessel were then closed with a continuous mattress suture of 000000 black braided silk‡ on an atraumatic Kalt needle and reinforced with a simple whip stitch of the same material. Finally, clamps were removed and the remaining segment measured again. Usually it was possible to carry out this procedure accurately and handily within a period twelve to fifteen minutes. The intervening segment of aorta was banded snugly with the previously prepared Polythene tape of 0.25 to 2.0 cm. width. The area was sprayed with a penicillin solution and extrapleuralized with interrupted 0000 black silk prior to closing the chest wall.

In some animals of this group an attempt was intentionally made to produce a sufficiently high degree of resistance to evoke cardiac failure. As a consequence several animals were obviously suffering from this complication in the postoperative period.

There were no deaths from primary or secondary hemorrhage in this group of animals. About 50 per cent of the puppies subsequently developed a significant coaretation; about 60 per cent of these coaretations were of a severe grade (Table IV).

RESULTS

Part I.—The successful production of a moderate to severe degree of coaretation of the thoracic aorta in ten dogs stimulated us to devise more efficient

*Polythene tubing, Form PHF, medical type, manufactured by Surprenant Manufacturing Company, Boston, Mass.

†Silicone Oil No. 9987, manufactured by General Electric, Schenectady, N. Y.

‡These were supplied through the courtesy of Johnson & Johnson, New Brunswick, N. J.

TABLE IV. COARCTATION OF THE AORTA PRODUCED BY WEDGING OR NOTCHING OF THE AORTA AND EXTRAVASCULAR FIBROPLASIA DUE TO POLYTHENE TAPE

Number of Dogs With Coarctation Produced		13
Moderate	4	
Severe	9	
Number of Unsatisfactory Results		12
Loss	0	
Disease	4	
Erosion	0	
Initial overocclusion of aorta	1	
Heart failure	6	
Empyema	1	
Operation or anesthesia	0	
Total Number of Animals Studied		25

methods. An analysis of the failures emphasized that most deaths were due to disease, postoperative empyema, and hemorrhage following erosion of the aorta by the compressive band. A summary of these cases has been presented in Table I.

Part II.—An appreciable improvement in the morbidity and mortality from disease followed the adoption of a carefully supervised program of animal care. Segregating young puppies from adult dogs reduced the exposure to viruses and bacteria. Passive and active immunization afforded a modicum of protection. These factors cumulatively lowered the death rate to about 15 per cent. With improved anesthesia routines and the instillation of intrapleural penicillin the incidence of empyema declined from 15 per cent to 2 per cent. The adoption of the notch resection or "wedging" removed the need for extensive compression by a banding tape. This permitted the loose application of a fibrogenic substance and diminished the number of deaths from erosion and hence from secondary hemorrhage. During initial experiments when the aorta was cross-clamped for but the rather brief periods (fifteen to thirty minutes) necessary for wedging or notching, there followed a temporary to permanent hindquarter paralysis in several dogs. This complication was avoided in all subsequent experiments by the use of a plastic tube shunting blood around the operative area.[53]

A deliberate overocclusion of the aorta was attempted in one series of experiments in order to determine the degree of tolerance to obstructed flow. This type of overocclusion produced two distinct syndromes: either a "mechanical" shocklike state leading to death within twenty-four hours, or a state of cardiac decompensation leading to death within two days to three weeks. After accumulating some experience we could predict which aortas were being overconstricted.

Five dogs died of overocclusion within four to twenty-four hours after operation. At autopsy there was an extreme congestion and a marked venous and capillary engorgement of all abdominal viscera. Frequently, diffuse petechial or gross focal hemorrhages were present over the visceral and parietal peritoneum, as well as in the splenic and hepatic subcapsular areas. Within the intestinal lumen, bloody mucus and superficial mucosal ulcerations were apparent. These erosions were largely limited to the terminal ileum and proximal colon. These lesions grossly resembled those seen in asphyxia neonatorum

and were similar to those previously described by Erlanger and Blalock.[40, 41] None of these animals demonstrated pulmonary edema, cardiac dilatation, or other signs of acute cardiac decompensation. The bladder contained dark clear urine. The nonprotein nitrogen was about 100 per cent in the two animals examined.

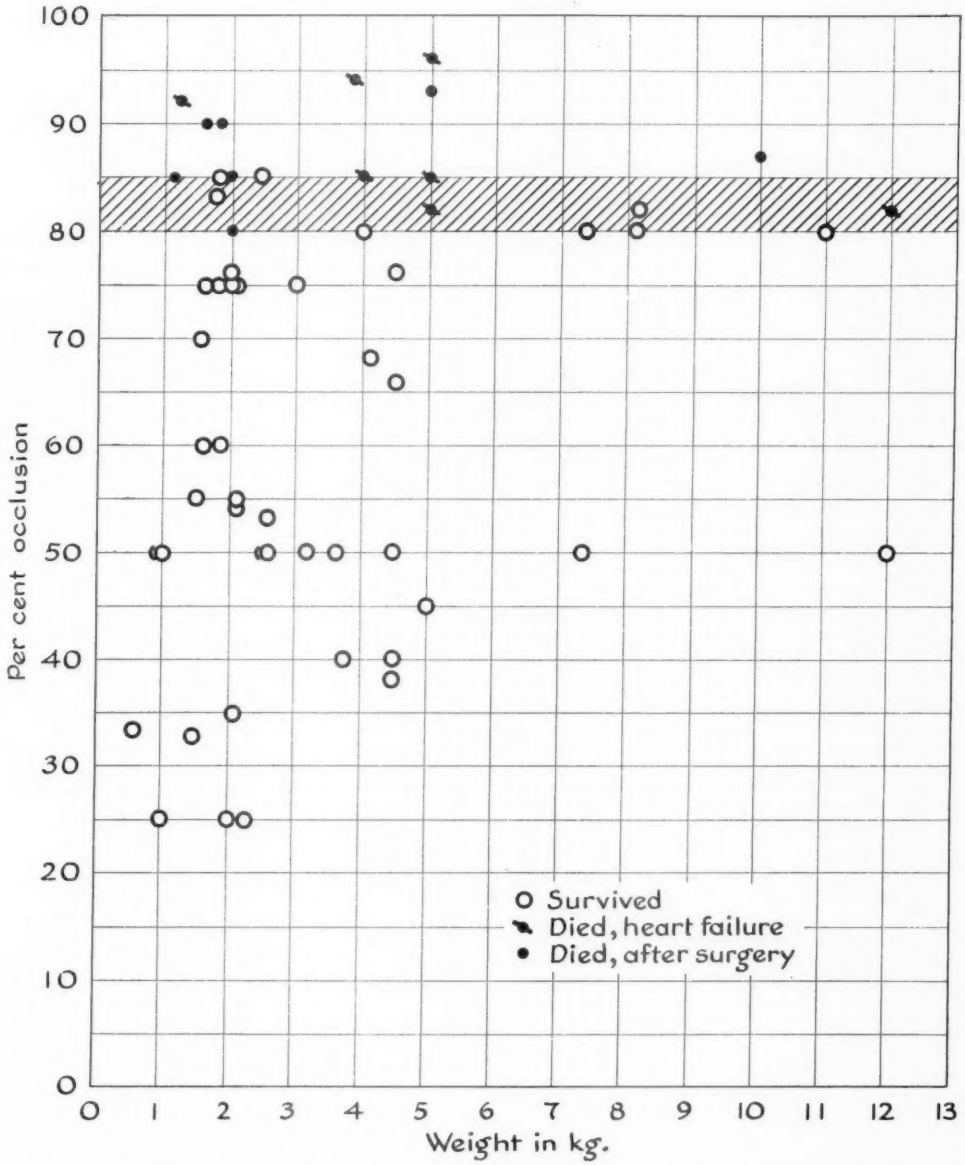


Fig. 4.—The fate of fifty-eight dogs following various degrees of initial occlusion of the proximal thoracic aorta. Note critical area between 80 and 85 per cent.

Six dogs died between the second and nineteenth postoperative days with signs and symptoms typical of progressive cardiac decompensation. At autopsy the serous cavities contained considerable amounts of thin hemorrhagic fluid. The viscera were congested. Hepatosplenomegaly was common. The tracheobronchial tree was filled with a thin bloody froth. The heart was

in the systolic phase, not dilated. The left ventricle showed evidence of muscular hypertrophy as determined both by inspection and by measurements of ventricular thickness and of total weight. The right ventricle was slightly thickened in only two instances.

A review of those instances in Part I in which the dogs died in the early postoperative period strongly suggests the "overocclusion" syndrome as the principal cause of death. Previously this had been overlooked. The result of various degrees of occlusion of the aorta is presented in Fig. 4.

In each instance the distended aorta was measured metrically in situ during surgery with Vernier calipers. A deduction was made for aortic wall thickness of 0.25 mm. for puppies of less than 5 kg., 0.5 mm. for those of 5 to 10 kg., and 1.0 mm. for larger dogs.

Upon post-mortem examination the length of the stenotic area was measured and the inside circumference determined by passing graduated French catheters through this area. By conversion to cross-sectional area in square millimeters the percentage of occlusion was readily calculated.

Instances in which the animals survived weeks after the intial operation it was necessary to measure both the normal aorta and stenotic area in a similar fashion.

As is apparent in Fig. 4, there were no deaths due to overocclusion in dogs with less than 80 per cent occlusion of the aorta; about one-half of the dogs survived with 80 to 85 per cent occlusion, and none lived with over 85 per cent occlusion.

The degree of stenosis following fibrogenic activity of "cigarette cellophane" and Polythene film varied. The Polythene was more easily handled and produced sufficient compressive fibrous tissue reaction in several instances to reduce the available vascular luminal area by 75 per cent within a period of four months (Fig. 5). In such instances a marked reaction was present around the tape. Microscopic sections (Fig. 6) taken through the area were characterized by thickening, edema, and cellular infiltration of the vessel wall and perivascular structures. The intima was thickened. In no instance have we seen the intense obliterative periarteritis reported by Pearse.

Control dogs banded with nonreactive Cellophane showed no luminal changes, and the microscopic sections (Fig. 6) through the banded area showed little evidence of inflammatory or foreign body reaction. The vessel wall beneath the band was often atrophic, with apparent migration of the band toward the vascular lumen.

Effect on the femoral pulse was carefully followed during the entire postoperative period. Examination by palpation was made at weekly intervals and a tactile evaluation of the degree of obstruction to the aortic blood flow estimated. In those animals with an initial occlusion in the range of 80 per cent, the femoral pulse was weak and the femoral artery small and cordlike. Later, as collateral channels developed, the artery swelled with blood under nearly normal tension but displayed only a slight or even impalpable pulse.

The treadmill was used to exercise three coarcted dogs in an attempt to increase the rate of collateralization. When compared with litter-mate con-

trol animals a striking difference was noted in the ability of the animals to sustain effort. A normal dog tolerated fifteen minutes on our treadmill with ease, whereas the coarcted animals did well for nine to twelve minutes, at which time the hind legs weakened and actually would drag limply behind the animal as he attempted to pull himself along with his forequarters.

In addition to periodic examination of the femoral pulses, ten animals were sacrificed or reoperated upon three to eighteen months after the initial operation. These dogs, together with six normal animals, have been the subjects for further studies of blood pressure and pulse wave. After anesthetizing these animals (35 mg. of sodium pentobarbital per kilogram of body weight),

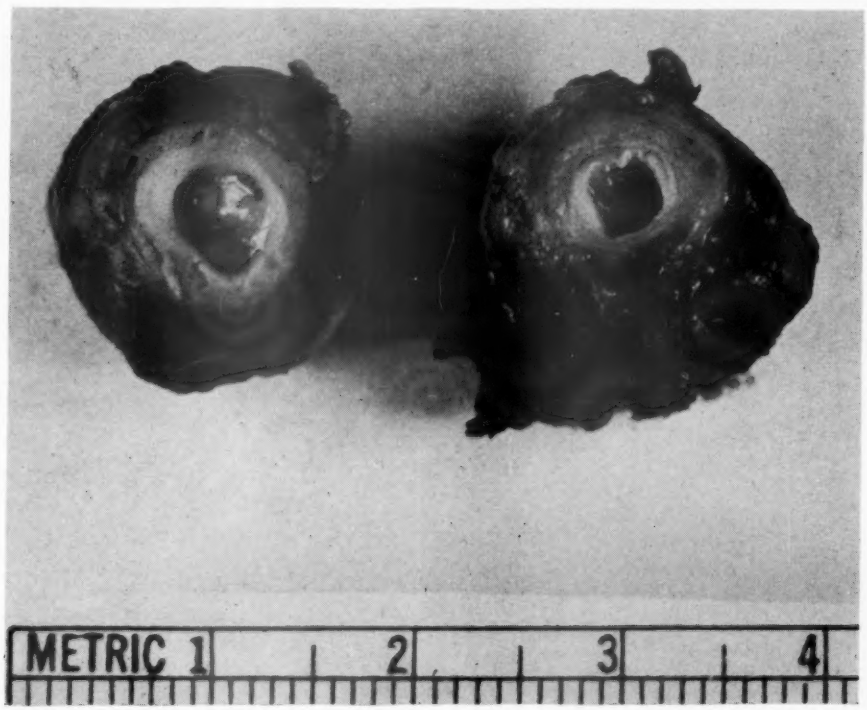
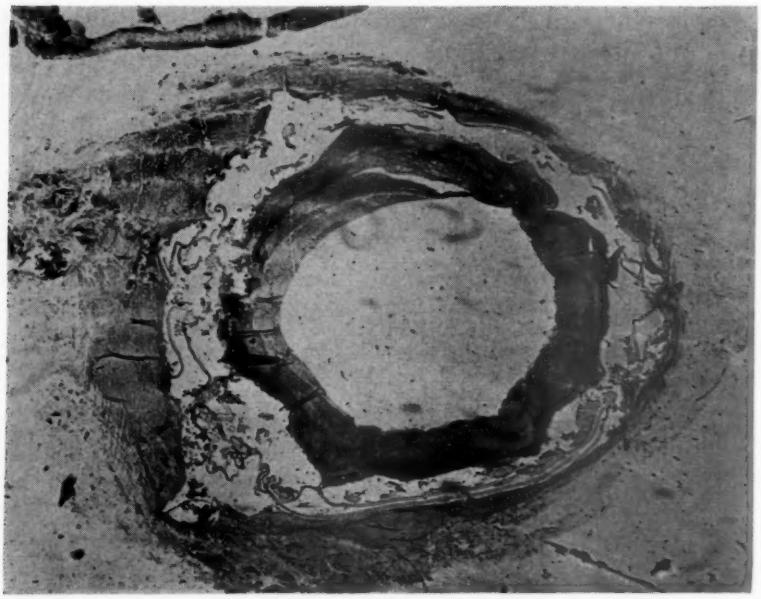


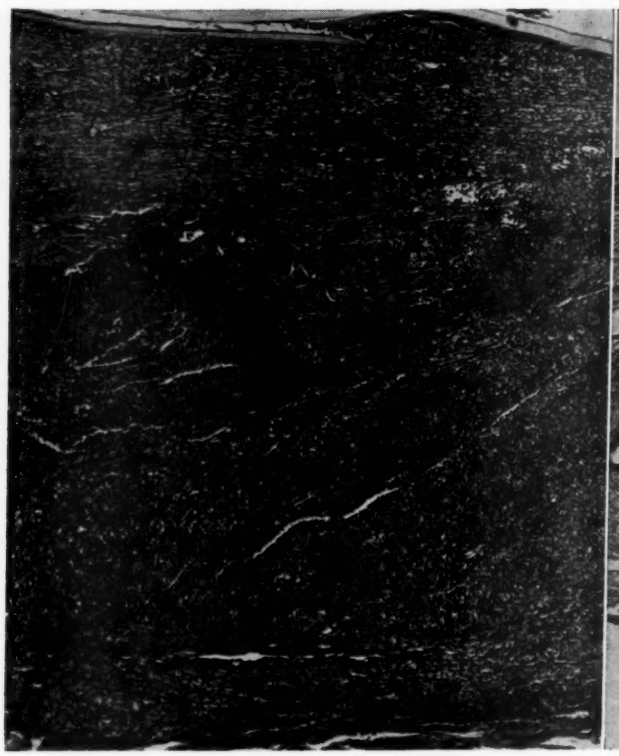
Fig. 5.—Segments of aorta removed at operation, showing area of atresia produced by a Polythene tape over fascia (left), and 91.8 per cent stenosis produced by wedging and Polythene tape (right).

simultaneous pulse tracings of the carotid and femoral arteries were made.* A No. 15 cannula was tied into the artery and connected to a pressure transmitter† by lead tubing; this recorded the pressure, which was magnified and transferred to the written record by a Brush multichannel oscillograph.‡ Tracings of a normal and several coarcted animals are presented in Fig. 7 and are summarized on Tables V and VI. The mean pressure readings were either calculated by planimetry or obtained by arterial puncture, measured with a mercury-filled U tube, and recorded kymographically on a smoked drum.

*With the cooperation of Mr. Wayne L. Adams of the Department of Physiology.
†Pressure Transmitter, Model P23B, Strathan Laboratories, Beverly Hills, Calif.
‡Brush Development Company, Cleveland, Ohio.



A.



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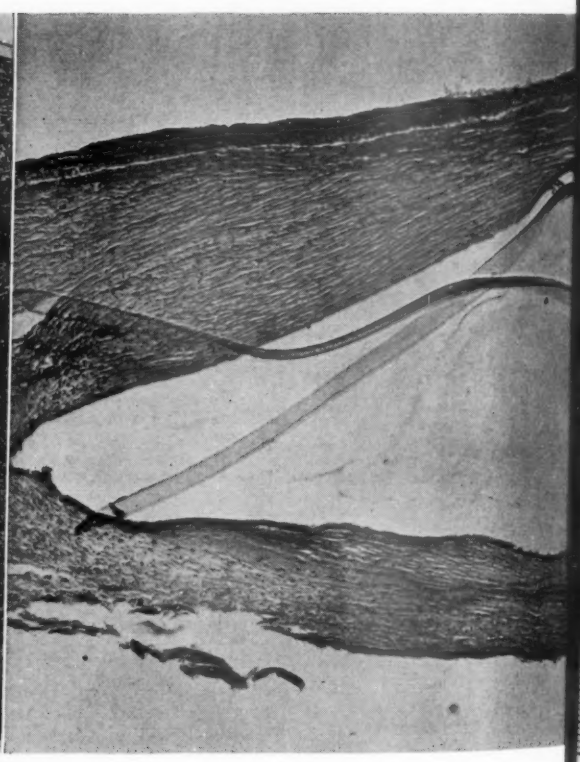


C.

Fig. 6.—*A*, Photomicrograph showing site of stenosis banded with Polythene tape; *B*, Photomicrograph showing marked inflammatory reaction in wall of aorta beneath Polythene band (visible at top of section) (four months) X; *C*, Photomicrograph showing minimal reaction associated with nonreactive Cellophane band which is actually migrating through aorta (three months) X.

Eight of the ten dogs with coarcted aortas were found to have hypertension as measured in the carotid artery and a significant difference in pressures between the carotid and femoral artery (Table VI). The degree of occlusion

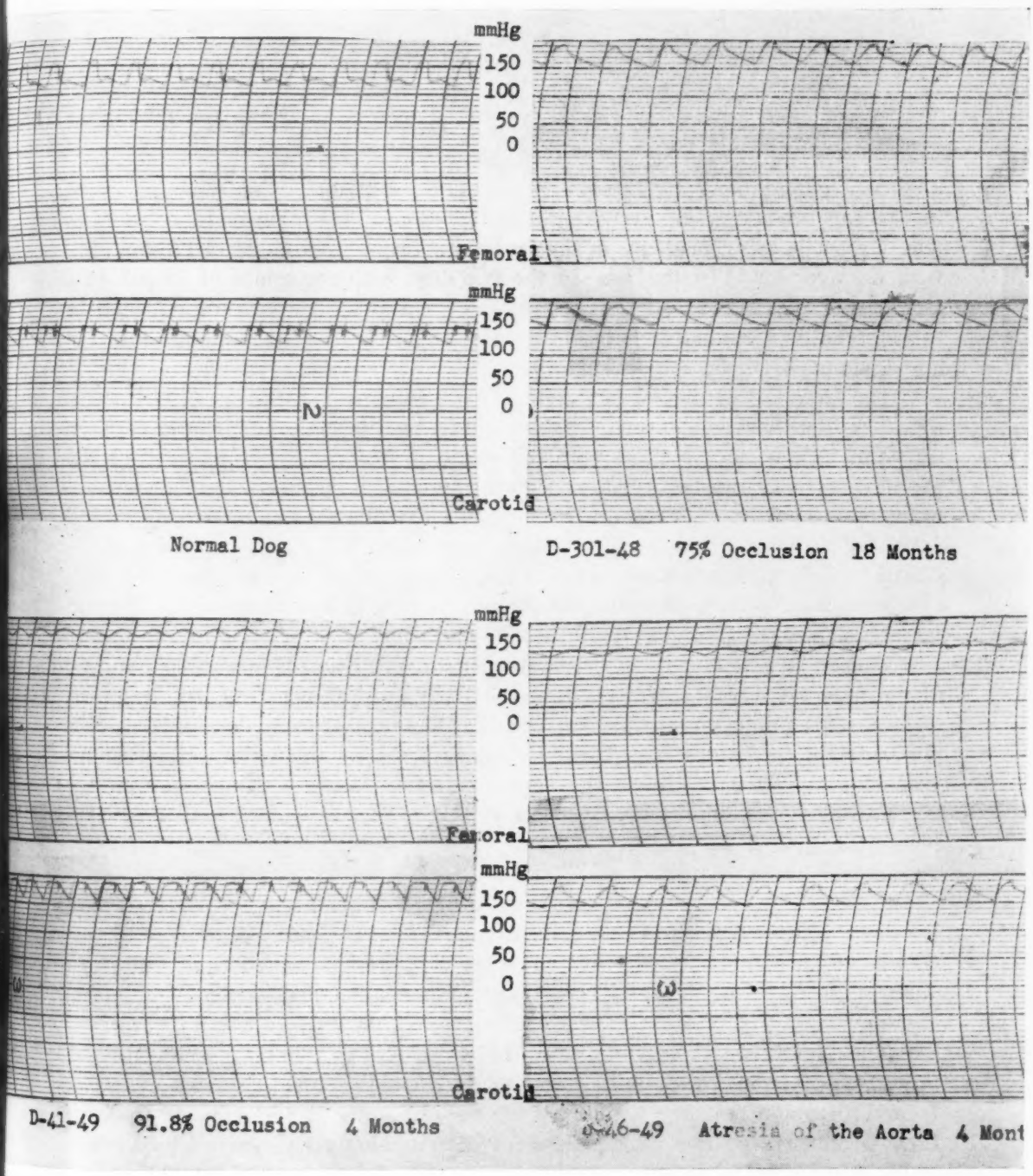


Fig. 7.—Oscillograph tracings of pulse wave in a normal dog and three dogs with various degrees of coarctation of the thoracic aorta.

TABLE V. BLOOD PRESSURE RECORDINGS ON SIX NORMAL DOGS (MM. HG)

DOG NUMBER	TIME LAG	"STRAIN" GAUGE PULSE TRACING		CALCULATED MEAN OR HG MANOMETER RECORDING		PULSE PRESSURE	
		CAROTID	FEMORAL	CAROTID	FEMORAL	CAROTID	FEMORAL
D-N-49				104	108		
D-N_2-49				136	140		
D-N_3-49				104	106		
D-N_4-49				126	126		
D-N-50		154/120	162/114	140	144	34	48
D-N_1-50	1/32′	130/112	144/120	128	132	24	24
Average				123	126	29	36

in these eight animals varied from 79 per cent to atresia. Their mean pressure in the carotid artery ranged from 168 to 242 mm. Hg; the average was 193 mm. Hg. The mean pressure in the femoral artery was from 94 to 176 mm. Hg with the average 149 mm. Hg. In the two dogs with occlusions of 62 per cent and 75 per cent the blood pressure in the femoral artery was higher than in the carotid. In six normal dogs the mean carotid pressure was 124 mm. Hg and 134 mm. Hg in the femoral artery.

The time lag in the femoral artery from the onset of the systolic wave to the apex of the wave measured 0.06 second in two normal animals and between 0.15 and 0.20 second in those with coarctation. The difference in onset of the systolic wave in the carotid and femoral arteries was 0.03 second in normal animals and 0.06 to 0.08 second in coarcted individuals. The pulse rate varied from 120 to 160 per minute during these recordings. The pulse pressure in the carotid artery was increased, ranging from 40 to 58 mm. Hg as compared with the normal of 30 mm. Hg. In the femoral artery it was reduced to 10 to 18 mm. Hg compared with normal of 24 to 48 mm. Hg.

The collateral circulation was studied on all animals on which detailed blood pressure records were obtained. By using 70 per cent Diodrast for arteriograms for in vivo studies, or with barium sulphate-agar agar mixture for post-mortem injections, satisfactory visualization of the collateral channels was possible. Dogs with less than approximately 75 per cent occlusion of the aorta did not develop collateral channels (Fig. 8). Instances with a greater percentage occlusion characteristically manifested the turbulent, tortuous, vascular channels of clinical coarctation (Fig. 8).

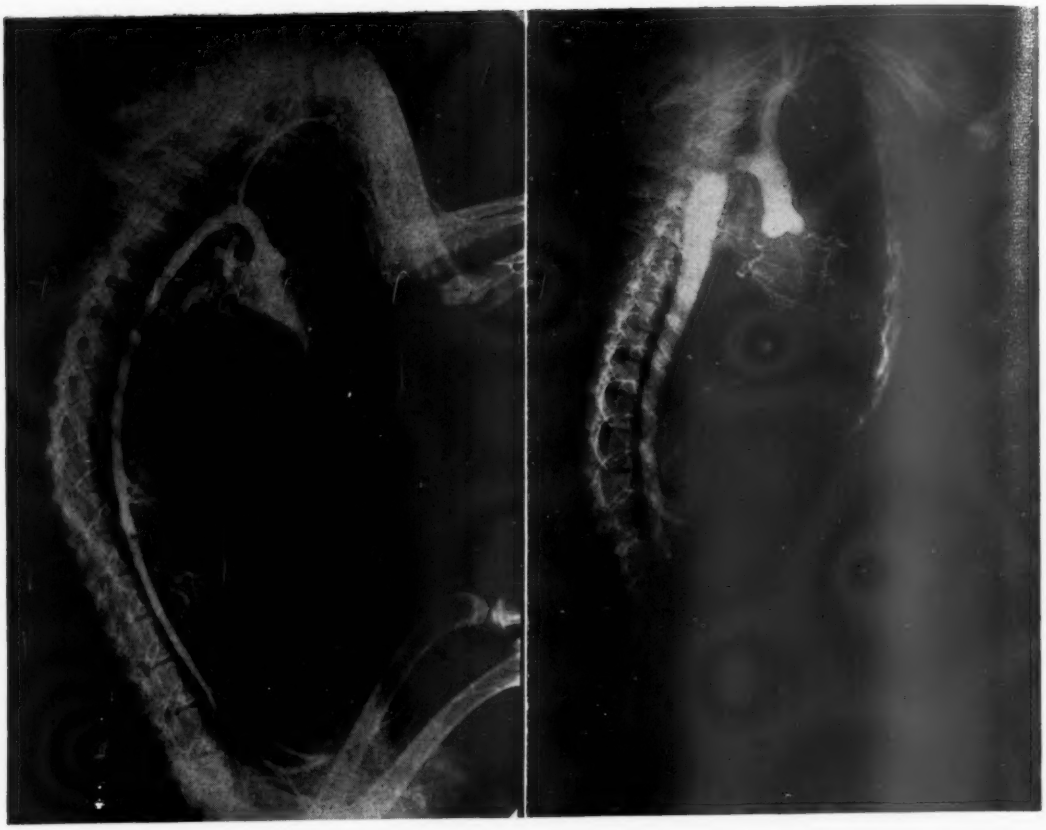
Cardiac hypertrophy, particularly of the left ventricular musculature, has been observed in those animals dying of overocclusion of the aorta. It was more marked in those dogs surviving a longer period of time, and most marked in those with the highest carotid pressures and/or least collateral channels (Fig. 9).

The fundi were examined* on three dogs subsequently sacrificed. Although each animal was later found to have mean carotid pressures ranging from 170 to 190 mm. Hg with diastolic pressures above 130 mm. Hg, none of them demonstrated those significant intraocular changes described by Owings in his animals with aortic atresia.

*By Dr. John P. Wendland of the Department of Ophthalmology.

TABLE VI. BLOOD PRESSURE RECORDINGS IN TEN DOGS WITH VARIOUS DEGREES OF COARCTATION OF THE AORTA (MM. HG)

DOG NUMBER	PER CENT OF COARCTATION	TIME POSTOP. (MONTHS)	ESTIMATED COLLATERALS	TIME LAG	STRAIN GAUGE PULSE TRACING		CALCULATED MEAN PRESSURE OR HG MANOMETER RECORDING		PULSE PRESSURE (MM. HG)	
					CAROTID	FEMORAL	CAROTID	FEMORAL	CAROTID	FEMORAL
D-58-49	62.0	4	0				152	164		
D-1-48	75.0	18	0	1/20′	190/148	198/150	168	180	42	48
D-52-49	79.0	4	+				184	176		
D-62-49	86.0	2	+				192	94		
D-61-49	91.5	3½	++				170	130		
D-41-49	91.8	4	+++	1/12′	192/152	188/170	170	156	40	18
D-77-49	92.0	3	++				190	150		
D-2-48	92.5	18	++				242	160		
D-67-49	95.0	3	+	1/16′	240/182	160/150	212	158	58	10
D-46-49	100.0	4	++++	1/12′	190/150	158/146	168	152	40	12
Average of 8 dogs with significant coarctation							193	149	46	13



A. *B.*

C. *D.*

Fig. 8. *(For legend see opposite page.)*

The relationship between the diameter of the aorta and the weight of the dog was obtained in seventy animals. A scatter graph summarizing this data is presented (Fig. 10).

Growth of the aorta early in a puppy's life appears to proceed at a rate more rapid than for the body as a whole. The importance of utilizing this fact is best shown by the picto-graph of the effect of growth alone on the aorta of a 2 kg. pup which reaches a weight of 15 kg. at maturity (Fig. 11).

Fig. 9.—Cardiac hypertrophy following partial occlusion of the thoracic aorta. Note relative thickness of musculature compared with lumen of left ventricle. Left, normal; right, 91.8 per cent occlusion (four months).

DISCUSSION

Experimentally induced coarctation of the thoracic aorta in dogs appears to resemble substantially the same lesion in man. This is corroborated by a comparison of our studies on dogs with those of Woodbury[54] and of Brown[55] on man. Comparable data are observed in pulse pressures, pulse waves, blood pressures, exercise tolerance, collateral circulation, and pathologic changes.

By studying such indirect evidence as blood pressure tracings, pulse waves, collateral circulation, and cardiac hypertrophy in dogs we have found little influence on the passage of blood through a stenotic area until that area is reduced to at least 25 per cent of the normal cross-sectional area or about 50 per cent of the normal intraluminal diameter.

Biologic tests in surviving dogs correlate closely with the flow studies made by Mann and co-workers.[45] It is reasonable to suspect that interchange-

Fig. 8.—Contrast media arteriograms made by injection of 70 per cent Diodrast or barium sulphate-agar mixture into common carotid artery. *A*, normal dog; *B*, 95 per cent occlusion of aorta; *C*, 95 per cent occlusion of aorta following resection of coarcted area (Diodrast study); and *D*, 91.8 per cent occlusion of aorta following resection. Death occurred in twenty-four hours due to overocclusion syndrome because of insufficient collateral circulation.

able hemodynamic principles apply in coarctation of the aorta both in man and in the dog. Corrective surgery for coarctation of the aorta in a growing child should be deferred until that time when, despite the limited additional growth at the anastomotic line, a relative coarctation shall not be produced. It is important to know, therefore, the relative rate of growth of the aorta in human beings. Scammon[48] has indicated that the growth of the cardiovascular system parallels that of the body as a whole. We have not found this to be the case in the aorta of dogs (Fig. 10). The correlation of body size with

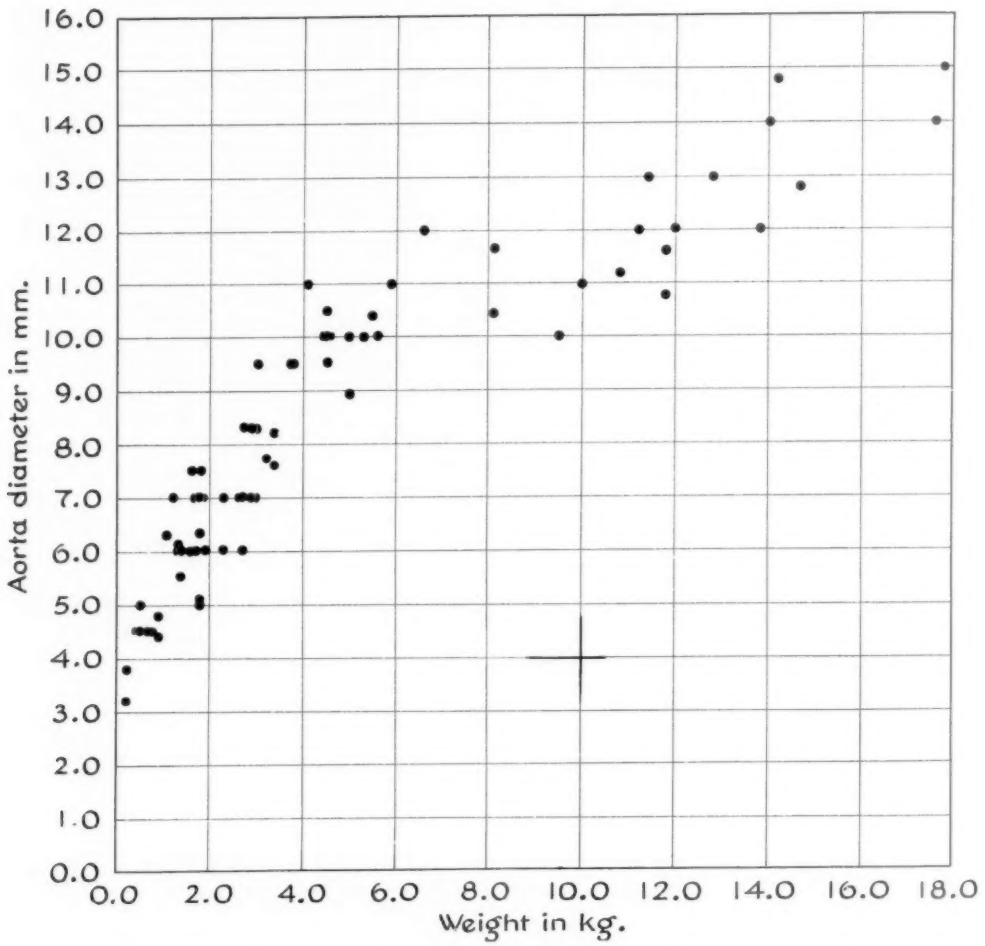


Fig. 10.—The outside diameter of the aorta of seventy dogs measured in situ at operation, compared with the dogs' weight.

aorta size in normal infants and children would be of value to clarify this point. Obversely, to withhold definitive corrective surgery in any child longer than is hydrodynamically ever to be required by growth demands, merely to reassure one's cautious self, is to court known disaster. Blackford[56] has appropriately emphasized that in 267 of 323 cases of coarctation reviewed by him the patients died before reaching the sixteenth year of life.

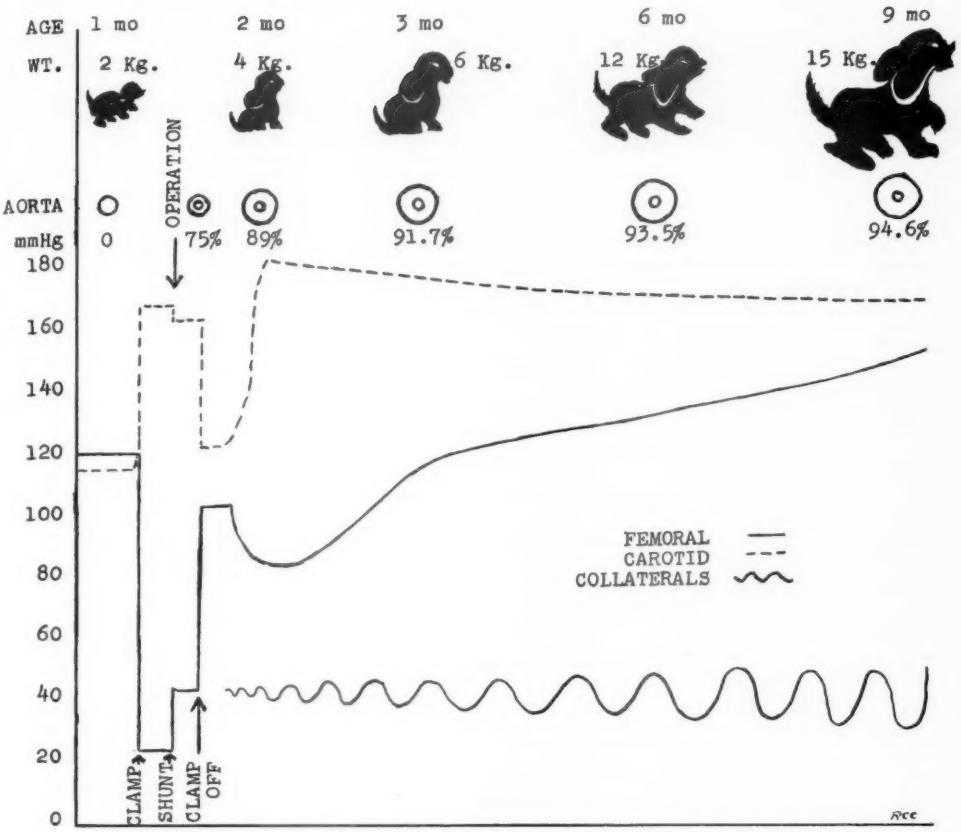


Fig. 11.—A schematic summary of the factors involved in the production of coarctation of the aorta in dogs by wedging or notching of the aorta plus growth.

CONCLUSIONS

1. A method for producing a high degree of coarctation of the aorta in young growing dogs is presented.

2. The factors concerned in this method are: (a) the immediate reduction of the cross-sectional area of the thoracic aorta by wedging or "notching" the vessel; (b) the progressive constrictive fibroplasia induced by encircling the remaining vessel with a fibrogenic plastic band; and (c) the subsequent disproportionate growth rate between the narrowed area and the adjacent vessel.

3. Coarctation of the aorta thus produced is physiologically, roentgenologically, and pathologically indistinguishable from similar lesions in man.

4. A satisfactory method of initially reducing the cross-sectional area of a large artery by means of "wedging" or "notching" is described.

5. The dangers of incomplete obliteration of large vessels by compressive devices is re-emphasized. That fibroplasia induced by plastic films beneath the compressive device will not safely protect the artery from atrophy and subsequent erosion has been demonstrated.

6. The use of a "buffer" substance, such as fascia lata, beneath the compressive band does not protect the vessel wall from atrophy and erosion.

7. A growth gradient for the normal functioning thoracic aorta in dogs is presented and its possible relationship to the surgical correction of coarctation of the aorta in infants and children is suggested.

8. The development of "mechanical shock" following the cross-clamping of the thoracic aorta has been confirmed and those secondary deleterious effects upon the spinal cord and viscera have been regularly prevented by the use of a small plastic tube for shunting blood around the clamped area.

9. The degree of initial occlusion of the proximal thoracic aorta that is tolerable in young dogs has been determined by biologic test.

10. A detailed regimen for the care and surgery of small puppies is outlined.

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DISCUSSION

DR. FRANK GERBODE.—We have been interested in producing experimental coarctation during the last two or three years, and published our method about two years ago. I will show you the method, and any of you who are interested in it will, I think, find it a very simple way of producing coarctation very much like that found in human beings.

(Slide.) This shows a puppy 36 hours old. We simply put a silk ligature around the aorta just beyond the left subclavian artery, and tied it loosely so that it could be moved on the aorta. This has to be done rather rapidly. One can get an intratracheal tube into these little puppies, and by using oral inflation of the lungs through a connecting rubber tube, the lungs can be inflated rhythmically. We have done several series in this manner.

(Slide.) This shows an angiogram of such a dog after one year, and a tracing of the roentgenogram on the right. The rich collateral circulation around the coarctation is quite evident. These animals also develop the distal dilation beyond the stenosis which is commonly found in human coarctation.

(Slide.) This shows the cardiac hypertrophy which developed in the experimental animal compared with a normal heart of the control animal of the same litter. You will notice the left ventricle as being the one that is thickened.

This shows the button of one of these coarctations removed after one and one-half years. On the left side it shows the 2 mm. opening allowed by the ligature. On the right side of the slide you see the same button turned over, showing the aorta completely closed off by another ligature tied firmly just distal to the first one, one and one-half years after the initial operation. The animal showed no ill effect from complete occlusion of the aorta.

We have done intra-arterial blood pressure determinations on all of these animals, and found the expected hypertension in the forelegs and a hypotension in the hind legs.

DR. W. C. SEALY.—Our group at Duke Hospital has been investigating the problem of experimental coarctation of the aorta primarily in order to study the physiologic effects of aortic constriction. We have used a Lucite tube with an hourglass shaped internal bore that is 4 cm. long and 3 mm. in its smallest internal diameter. This tube is inserted into the first portion of the descending aorta of the dog.

In the adult dog hypertension is produced above the constriction; in some instances, usually three to six weeks after constriction, it rises to 300 systolic and 200 diastolic. In addition, hypertension occurs below the constriction about this time, though not to the extent of that above the constriction.

The possible role of changes in renal blood flow in the development of hypertension after aortic constriction was studied by renal clearances of insulin and para-aminohippurate. In some of the animals, immediately after constriction, there was a decrease in renal blood flow, and in others, no change. No relation between the hypertension and renal blood flow has been established, as the hypertension in some animals has progressed after the renal blood flow has returned to normal.

Studies in patients after removal of the constriction have presented an opportunity for investigation of the effects of removal of the constriction. Dr. Clark presented his findings yesterday. Our studies in patients have paralleled those in dogs in that we could not correlate the changes in renal blood flow with the changes in the blood pressure level.

DR. R. L. VARCO (Closing).—On behalf of Dr. Clatworthy and the other co-authors, I wish to acknowledge an appreciation of both Dr. Gerbode's and Dr. Sealy's comments, as well as indicate that the limitation of time has imposed some difficulties in presenting the whole problem. We hope this situation will become more apparent on the perusal of the entire paper.

Suffice it to say that in answer to Dr. Sealy's implication, hypertension, both of the diastolic and systolic components, was quite as great in the animals in our experiments as it was in the experiences he has reported. In our preparations, systolic pressures over 250 mm. of mercury have been recorded by electronic methods, and diastolic values well over 160 mm. of mercury have been measured.

On this occasion I would like also to indicate it is my feeling that the type of shock and deterioration of the experimental animal reported by Dr. Gerbode after cross-clamping the inferior vena cava is quite conceivably related to the mechanical shock described by Erlanger and by Blalock. This situation would probably be obviated in a predictable fashion by the use of a shunt. As was shown in the earlier slides with a shunt around the cross-clamped aorta, mechanical shock fails to appear even after several hours. Similarly, if one were to shunt past the cross-clamped inferior vena cava to the superior vena cava, I surmise that the condition of mechanical shock, as it probably occurred in his animals, would be avoided.

A FUNCTIONAL STUDY OF AFFERENT FIBERS IN PERIPHERAL SYMPATHETIC NERVES

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Leo R. Radigan, M.D., Indianapolis, Ind.

(From the Department of Surgery, Indiana University School of Medicine)

SYMPATHETIC denervation of the extremities often brings almost dramatic relief from pain in patients suffering from various vascular disorders, causalgia, and related difficulties. When such relief from pain occurs in ischemic limbs, the circulation of which is improved by the sympathetic interruption, one may logically explain the benefit of the procedure upon the basis of elimination of efferent sympathetic impulses and consequent increase in blood flow. When, however, pain is relieved without demonstrable improvement in circulation, as sometimes occurs in severe obliterative arterial disease, or in instances in which the circulation to the affected part is already excellent, as is often true, for example, in causalgia, such an explanation seems untenable.

The simplest manner in which the mechanism could be explained would be the assumption that afferent pain fibers are interrupted by sympathectomy or sympathetic anesthesia. The lack of convincing evidence that there are afferent fibers in the peripheral sympathetics has necessitated the postulation of theories to account for such relief of pain. Elsewhere one of us[1] has discussed this general problem, pointed out some of the apparent deficiencies in such theoretical explanations, and mentioned certain clinical observations which, though offering no conclusive proof, are highly suggestive that afferent pain fibers are present in the sympathetic nerves.

For several years we have been engaged in experimental studies designed to elucidate this problem.[2] Two observations proved of considerable interest and laid the foundation for the present investigation. First, the injection of an irritating solution into an isolated segment of a dog's femoral vein causes reflex vasoconstriction not only in the ipsilateral extremity, as was shown by Ochsner and DeBakey in their experimental study of vasoconstriction in thrombophlebitis,[3] but in the contralateral extremity as well. Secondly, the impedance pulsimeter or plethysmograph provides a particularly suitable method for recording changes in vasomotor status. This apparatus records graphically a true impression of vascular activity, the tracing corresponding closely to that of the volume pulse (Fig. 1).

MATERIALS AND METHODS

Healthy mongrel dogs were used. Several weeks before they were studied some of them were subjected to a left sympathetic denervation. These operations

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were performed aseptically under intravenously administered pentobarbital sodium anesthesia. The lumbar sympathetic chain was approached extraperitoneally, the dorsal chain transthoracically.

The pain experiments were also performed under pentobarbital anesthesia, 25 mg. per kilogram of body weight. The dogs were placed on a table on their backs in as comfortable a position as was possible. Care was taken in securing the extremities to avoid tight, constricting bands which might give rise to painful impulses during the study. The right hindlimb was left free. After the foot was shaved, the four small surface electrodes were placed, two proximally,

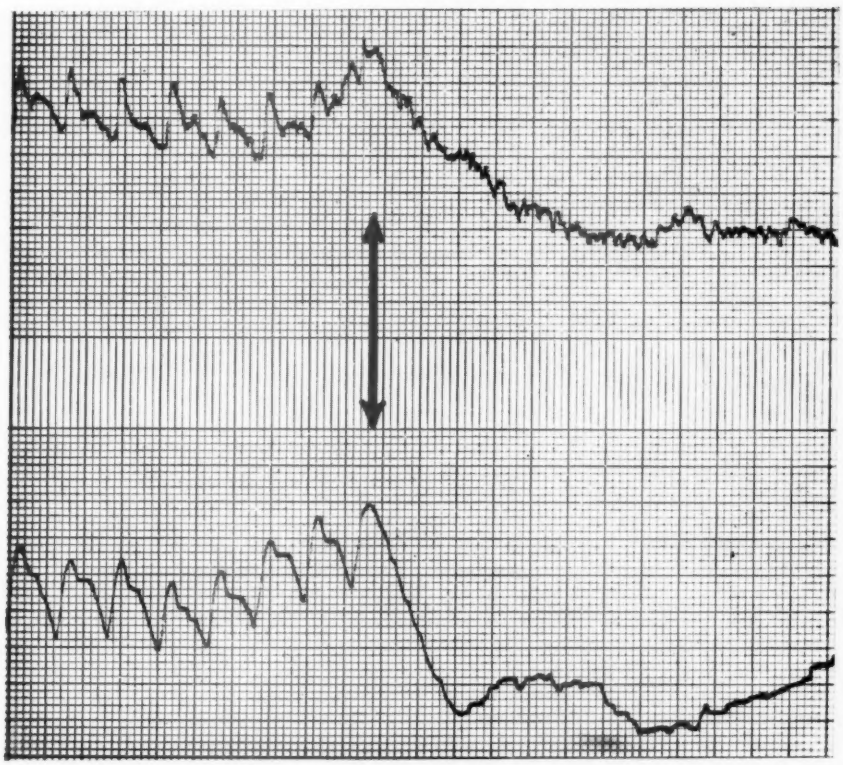

Fig. 1.—Simultaneous records of pulse volume obtained from third and fourth fingers with digital plethysmograph (top record) and impedance plethysmograph (bottom record). At the point indicated by the arrow, the brachial artery was occluded manually. The similarity of the two curves and the response to brachial occlusion is apparent. The digital plethysmographic record was made with a water-filled system leading from a digital cuff to an electromanometer.

two distally, one of each on the dorsal and one of each on the plantar surface, the two sets being about 3 cm. apart. Electrode jelly was used to insure good contact and the electrodes were fixed in place with small strips of adhesive tape. The electrodes were attached to the input cables of the impedance plethysmograph. The changes in impedance were recorded by means of a Poly-viso Cardiette, the sensitivity of which was not altered during any experiment. The impedance plethysmograph was carefully balanced before each run.

Two dogs, thus prepared, were used as controls for anesthesia. Frequent plethysmographic tracings were made over a period of one and one-half hours.

In three dogs, which served as controls for operation, the skin and subcutaneous tissue overlying the proximal portion of the left femoral vessels and the left cartoid artery were infiltrated carefully with 1½ per cent Metycaine. Longitudinal incisions were made and with as little trauma as possible the femoral vein and the carotid artery were exposed. The carotid artery was cannulated and attached to a mercury manometer. Both wounds were kept moistened with physiologic saline solution throughout the experiment. Again frequent tracings were made. In seven dogs the cartoid artery was similarly cannulated and the

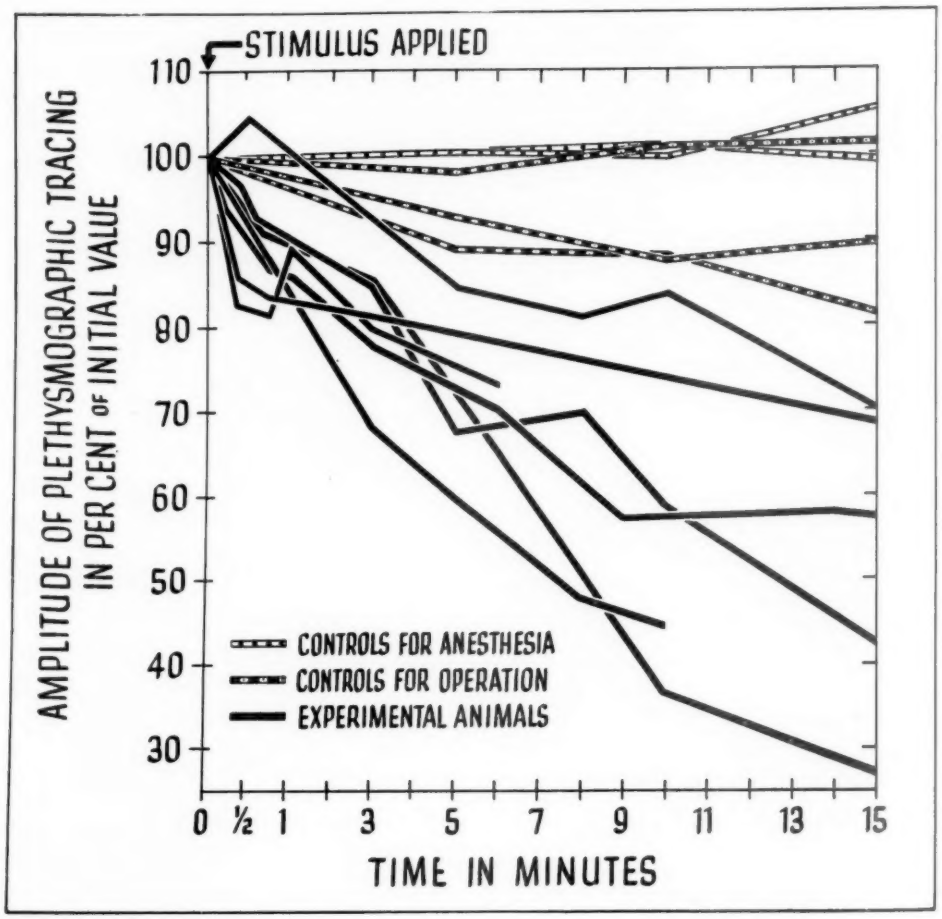

Fig. 2.—Records of changes in amplitude of plethysmographic tracings of the right foot of experimental animals after distention of a segment of the left femoral vein with an irritating solution compared with records of changes obtained from animals serving as controls for anesthesia and operation.

femoral vein, exposed in precisely the same manner, was ligated proximally near the point of reception of the profunda femoris. It was ligated about 3 cm. distally about a blunt metal cannula of small size which was introduced into the segment isolated by ligatures. The cannula was connected to a pressure bottle containing 20 per cent sodium salicylate solution. After obtaining initial plethysmographic tracings the segment of vein was distended with the salicylate solution to a pressure of 200 mm. of mercury. Frequent tracings were made

after application of this stimulus. The fourth group of eight animals were handled in exactly the same manner. They differed only in that they had previously undergone a left sympathetic denervation. The extent of the denervation was carefully checked after the experiment was completed and the dog sacrificed.

The impedance plethysmograph designed and built for us* was based upon the original instrument of Du Bois and Nims.[4] It permits balancing before each run and can be calibrated and quantitated easily.

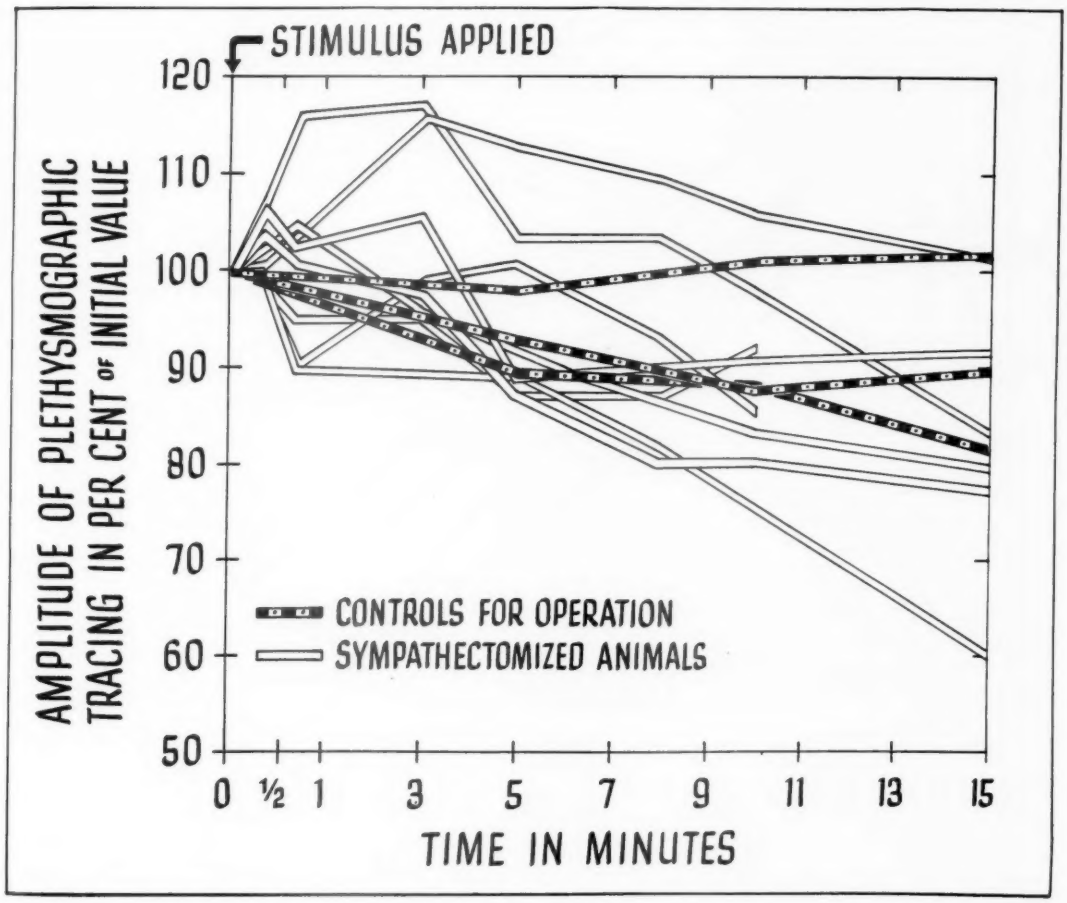

Fig. 3.—Records of changes in amplitude of plethysmographic tracings in animals previously subjected to sympathectomy after application of the stimulus of distention of the vein compared with tracings from animals serving as operative controls.

RESULTS

The plethysmographic changes which followed stimulation by distension of the vein with salicylate solution occurred quickly and the most significant changes occurred within the first fifteen minutes. During this period the anesthetic control animals showed a relatively constant amplitude of pulsations. The animals in which the femoral vein was exposed showed a slight tendency to contralateral vasoconstriction after a time but it is doubtful that this small change

*By Mr. George Siddons.

is of any significance when related to the rest of the data (Figs. 2 and 5). Following application of the stimulus the animals with normally innervated extremities showed a quick and significant drop in pulse amplitude in the contralateral foot (Figs. 2 and 4). It is seen that the general response in these animals duplicates closely the findings observed in controls which had not been given the irritating stimulus. The observations are summarized in Fig. 5 in

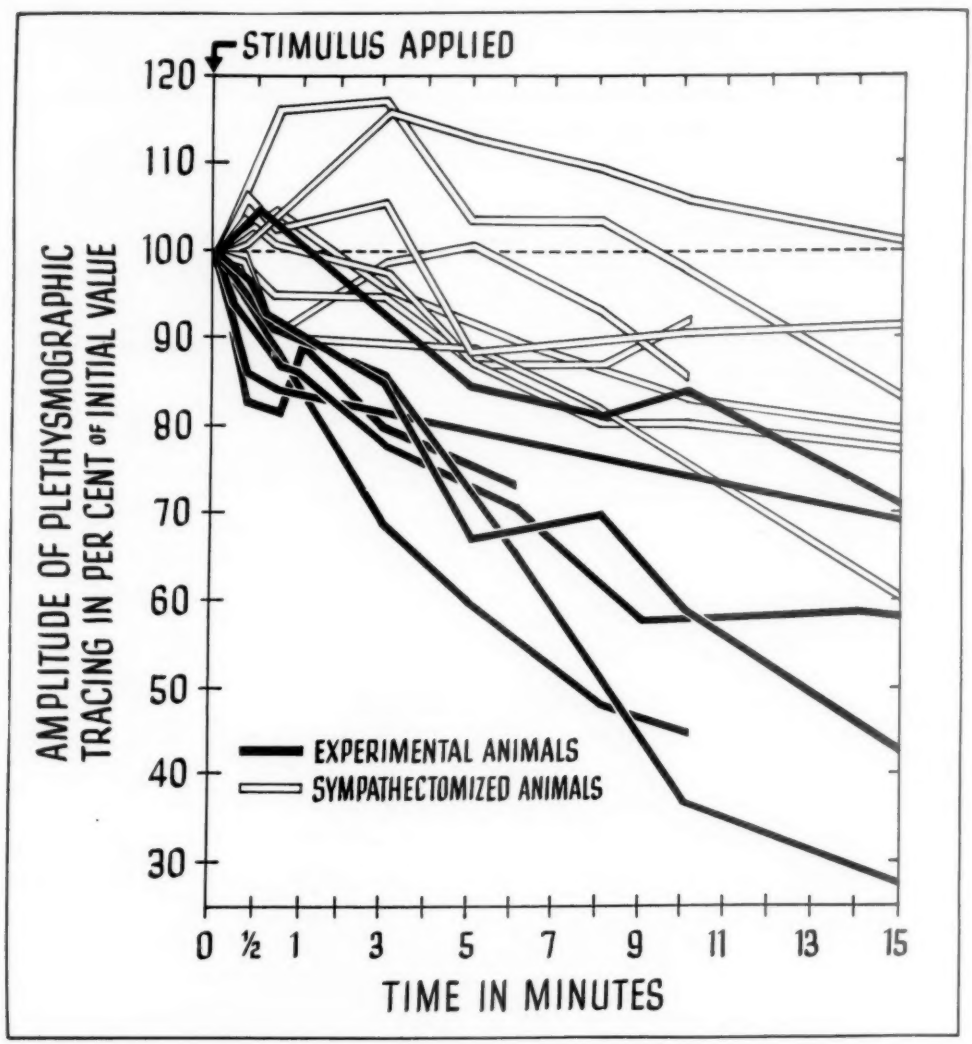

Fig. 4.—Records of changes in amplitude of plethysmographic tracings after application of painful stimulus in animals with normally innervated extremity compared with records of changes in animals with sympathetically denervated extremity.

which the average results of all the groups are charted. Analysis of the figures in the early phases of the experiments by determination of a critical ratio showed that a highly significant response occurred after the irritant solution had been instilled in those animals with intact sympathetic nerves but that no significant change occurred when the sympathetic chain had been interrupted.

In none of the animals included in this study did any significant alteration of blood pressure occur during the course of the experiment. Examination after

sacrificing the animals confirmed the operative removal of the sympathetic chain including from the ninth dorsal to the first lumbar vertebra at the upper limit and down to and including the fourth lumbar vertebra at the lower limit.

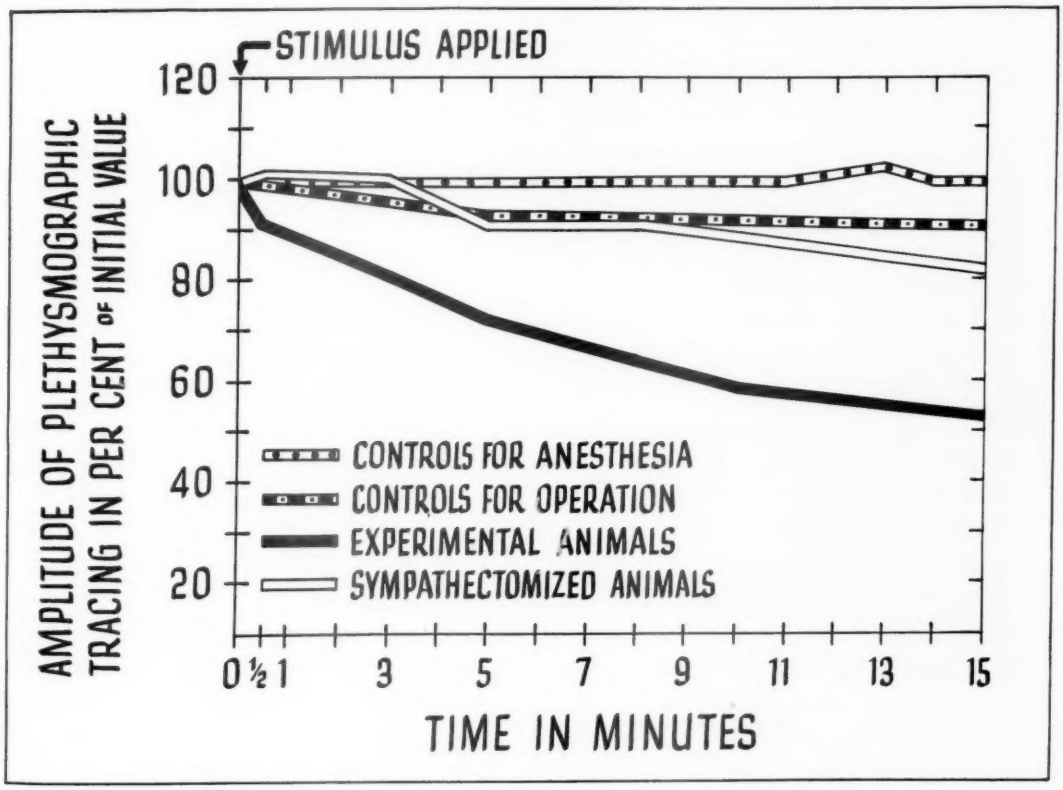

Fig. 5.—Comparison of mean changes in amplitude of plethysmographic tracings in the four groups of animals studied.

DISCUSSION

These experiments demonstrate that the vasoconstrictor response in the dog's right foot to the distention under pressure of a segment of the left femoral vein with 20 per cent sodium salicylate is abolished by left sympathetic denervation. No other conclusion is logical than that this abolition of response is effected by interruption of afferent fibers in the sympathetic chain. Any other conceivable explanation is so complicated and farfetched as to appear entirely unlikely. We are not concerned with the question whether any afferent fibers reaching the central nervous system via the sympathetic nerves belong generically to the autonomic or somatic nervous systems. If they are present in the sympathetic nerves they are from the gross anatomic, surgical, and over-all clinical standpoints sympathetic.

Confirmatory evidence of the presence of afferent fibers in the peripheral sympathetics is found in the excellent studies of Kuntz and Farnsworth.[5] They felt that there was good histologic evidence of such fibers and concluded, "Any

operation which effectively eliminates the vasomotor innervation of an extremity must also divide a goodly number of afferent fibers supplying the blood vessels and other sympathetically innervated tissues in the area affected." Dogiel[6] is said to have demonstrated both motor and sensory nerve cells in the stellate ganglia of dogs. Threadgill[7] also has recently reported some experiments from which he concluded that there were sympathetic afferent fibers. The reaction elicited from intense burning in an anesthetic limb was abolished following excision of the sympathetic chain. In addition, the blood pressure response following intra-arterial injection of sodium lactate was not altered by anterior and posterior root section in his animals, but was nullified when the sympathetic chain was removed. Unfortunately, these conclusions were drawn from experiments on only four animals and we have been unsuccessful in duplicating the same results.

The work of Moore and Singleton[8] and of Burget and Livingston[9] has frequently been referred to as demonstrating the absence of sympathetic afferent pain fibers. With both groups the technique of intra-arterial injection of an irritating solution resulted in objective evidence of a painful response. This reaction was abolished only after somatic anesthesia was produced, and was not altered by sympathectomy. These experiments are clear-cut and easily reduplicated. However, when the irritating solution is held within the artery, no response is obtained. Naturally the question arises then whether this type of stimulus may be legitimately interpreted as giving rise to "sympathetic pain," or whether the solution actually stimulates somatic nerves in the capillary bed or, by diffusion, stimulates somatic nerve endings outside the vascular bed.

Indeed, after the most intense efforts to devise proper experiments for study of this problem, using various stimuli and methods of studying the response, we feel that the crux of the problem lies in the choice of a stimulus which will actually stimulate any afferent nerve fibers which may be present in the peripheral sympathetics without at the same time stimulating somatic nerves. We feel that we have been fortunate in selecting such a stimulus and in securing an adequate means of recording the response.

CONCLUSIONS

Experiments are reported demonstrating that the contralateral vasoconstriction which follows distention of a segment of femoral vein with an irritating solution is abolished by ipsilateral sympathectomy. It is felt that these results can be properly interpreted as giving evidence that afferent fibers enter the central nervous system via the peripheral sympathetic nerves and the ganglionated paravertebral chain.

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DISCUSSION

DR. F. A. SIMEONE.—I want to express to the authors how much I have appreciated hearing this report. It is a nice piece of work and the results have an important bearing upon the old question of sensory fibers in the sympathetic nervous system, whether we consider them bona fide sympathetic fibers or hitchhikers. In our laboratories, we have been interested on the arterial side of this problem. So far as the arteries are concerned, we have not been able to record reflex effects upon irrigating a segment of artery with appropriate solutions unless we allowed the irritating solutions to enter the tissues. There, it is possible that afferent impulses may reach the central nervous system by excitation of the somatic fibers in the skin and muscles. Moore and Singleton made similar observations.

More recently Dr. James C. White, Dr. William Sweet, and I have been interested in pain fibers in the sympathetic trunks in man. We have placed electrodes on the lumbar sympathetic chain at levels between L-2 and L-4, and have stimulated the chain, having blocked it peripherally.

In two patients the stimulation was done when the patient had been allowed to awaken from cyclopropane or Pentothal Sodium anesthesia. These two patients complained of pain in the ipsilateral hypogastrium. One of them said that he had pain in the "crotch," but when he was asked a couple of days later where his crotch was he pointed to his hypogastrium. That was the closest to pain coming from the limbs which we could get.

In two other patients, the shielded electrodes were placed upon the sympathetic trunk and stimulated electrically two to four days after the day of operation. These patients also had pain in the ipsilateral hypogastrium. None experienced pain in the limbs.

SOME PHYSIOLOGIC EFFECTS OF LUMBODORSAL SYMPATHECTOMY FOR HYPERTENSION

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THE recent literature contains numerous reports dealing with the clinical appraisal of lumbodorsal sympathectomy for hypertension.[5, 16, 20, 21, 27] Relatively few of them, however, are concerned with the physiologic effects of the operation in man other than on the blood pressure. Of these, the earliest were studies of the effects of the operation upon the blood flow through the kidney, and this is understandable in view of the attention focused upon the renal blood flow by the early observations of Goldblatt and his associates.[12]

In 1940, Alving and co-workers[1] reported their studies of 8 patients who had had total sympathectomy for hypertension. They found diminutions in the vital capacity, and no important change in the cardiac output. In 1 of 5 patients studied they found evidence suggesting a relaxation of the efferent glomerular arterioles which resulted in an increased renal blood flow. In the other 4 there was either no significant change in the renal blood flow or a diminution. Corcoran and Page[3] reported Diodrast and inulin clearances in 2 patients before and after lumbodorsal sympathectomy. They observed a drop in the renal blood flow in both cases and a rise in the filtration fraction in 1 of them. Foa and associates[8, 9, 10] found that hypertensive patients had a lower effective renal blood flow and glomerular filtration rate and a higher filtration fraction than normal individuals. They found for hypertensives a high ratio for the filtration rate to tubular excretory mass and a low ratio for the renal blood flow to tubular excretory mass. Five to 12 months after operation no significant change in the renal blood flow data was evident even though the patients had experienced a lowering of the blood pressure following supradiaphragmatic splanchnicectomy and ganglionectomy as described by Peet. They assumed from these observations that the operation must have induced a decrease in the resistance offered by the renal vessels since the clearances were approximately the same as they were preoperatively in spite of a lower systemic blood pressure. They suggested that a study of the renal blood flow might serve as a better prognostic index than other excretory tests of renal function.

Talbott and associates[29] studied the renal blood flow by means of Diodrast and inulin clearance and correlated the findings with the renal histologic changes observed in kidney specimens removed for biopsy at the time of sympathectomy. Their findings were similar to those of Foa and co-workers.[10] There was a good correlation between their findings and the degree of histologic change in the kidneys, the degree of retinal changes observed ophthalmoscopically, and the fifteen-minute excretion of phenolsulfonephthalein. After studying the same

This work was supported in part by a grant from the Life Insurance Medical Research Fund and in part by a grant from the United States Public Health Service.

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patients late postoperatively, they concluded that "There was no significant difference in filtration rate or renal plasma flow following bilateral sympathectomy after circulatory adjustments had been made." Goldring and Chasis[13] described the effect upon the renal plasma flow in five hypertensive patients before and after sympathectomy. They likewise found no increase in renal blood flow following the sympathectomy.

The first report of the effects of lumbodorsal sympathectomy for hypertension upon the fluid compartments of the body is that of Freis and Smithwick[11] who studied the changes in blood and "available fluid" volumes in 10 patients who had lumbodorsal sympathectomy for essential hypertension. They observed a reduction in the total blood volume in 9 of the cases during the immediate postoperative period and attributed it, for the most part, to a reduction of the red blood cell volume. Six months later, the blood volume had returned to normal in 4 of the patients studied at the end of that time. They observed a slight reduction of the hematocrit value during the late period, but it was made up by a compensatory increase in the plasma volume. The greatest changes were found in the "available fluid volume," which increased strikingly during the early postoperative period, but returned later to the preoperative values in the 5 patients examined. They concluded that "The reduction in blood pressure following sympathectomy is not dependent upon changes in total blood or 'available fluid volume.' "

Wilkins, Culbertson, and Smithwick[30] studied the effects of various types of lumbodorsal sympathectomy upon the vasopressor responses of patients to standard stimuli. In particular, they found that the rebound observed preoperatively following brief periods of induced hypotension was decreased or abolished after operation in proportion to the extent of sympathectomy. In addition, employing the technique described by Bradley, and coworkers,[2] Wilkins, Culbertson, and Halperin[31] observed an increase in the hepatic blood flow early after operation, with a return to normal later. Even late after sympathectomy, however, the reduction in hepatic blood flow which followed the assumption of erect posture before the operation was absent or decreased.

During the past 3 years, a comprehensive study of the clinical and physiologic effects of sympathectomy for hypertension has been carried out at the Massachusetts General Hospital. The results for the blood pressure have already been reported.[6] Data concerning clinical responses other than those of the blood pressure are still undergoing analysis. It is the purpose of this report to describe some physiologic changes which take place after lumbodorsal sympathectomy for hypertension in man, namely, the effect upon the insulin tolerance, the bromsulfalein excretion as a measure of liver function, the blood and thiocyanate space volumes, and the renal blood flow.

METHODS

The studies were done upon ward and private patients of both sexes. The cases form a selected group in so far as only nondiabetic patients with hypertension who were judged clinically suitable for sympathectomy were included. All tests were done with the patients recumbent, after they had

fasted for 12 to 14 hours. Chemical determinations were done in duplicate. Insulin tolerance curves, the responses to the intravenous injection of 0.08 unit of insulin per kilogram of body weight, were constructed as described in a previous report.[25] All sympathectomies were done with intratracheal ether anesthesia.

The plasma and "thiocyanate space" volumes were computed by calculating the dilution of 10 c.c. of 0.1 per cent Evans blue dye (T 1824) and of 0.5 Gm. of sodium thiocyanate injected simultaneously.[14] The disappearance curve for Evans blue was plotted semilogarithmically from 4 concentrations measured at approximately 20 minute intervals from the time of injection. The total blood volume and the total red blood cell volume were calculated from the plasma volume and the hematocrit value observed after centrifuging the heparinized blood for 30 minutes at 2,000 revolutions per minute. Equilibration of the thiocyanate was considered to be complete by the end of 80 minutes after injection. Concentrations between this time and 120 minutes fell on a horizontal line. The "extravascular thiocyanate space" represents the total calculated thiocyanate volume minus the plasma volume. It probably approximates the interstitial fluid volume closely. All values were corrected to a standard surface area of 1.73 square meters.

The clearance of bromsulfalein from the blood is a useful measure of one of the functions of the liver.[19] The test was begun directly after obtaining the last specimen of blood for the thiocyanate determination. A single dose of the dye was injected intravenously. The amount injected was 5 mg. per kilogram of body weight, which in this group of patients amounted to very nearly 200 mg. per square meter of surface area. The amount remaining in the circulation at the end of 45 minutes was calculated by measuring the plasma concentration of the dye and multiplying it by the plasma volume. The fraction of the total amount injected which was retained in the plasma was then calculated and the results expressed as per cent retention. The Evelyn photoelectric colorimeter was used for the determinations.

Renal hemodynamics were studied by measuring the clearances of mannitol and sodium para-aminohippurate* as described by Goldring and Chasis[13] and Smith and associates.[26] All patients were in the fasting state when tested. Chemical determinations were done in duplicate and the final values obtained were all corrected to a standard surface area of 1.73 square meters. The examinations were done preoperatively and 10 to 15 days after completion of the operation. None of the patients has been studied late after operation.

RESULTS

Insulin Tolerance

Insulin Tolerance in Normotensive Patients.—The insulin tolerance of nonhypertensive subjects was tested by selecting 53 patients on the general hospital wards who had neither hypertension nor diabetes and were in the hospital for minor surgical problems. Patients with evidence of infection were

*Ampules of Mannitol and Sodium Para-Aminohippurate were supplied through the courtesy of Sharp & Dohme, Inc., Philadelphia, Pa.

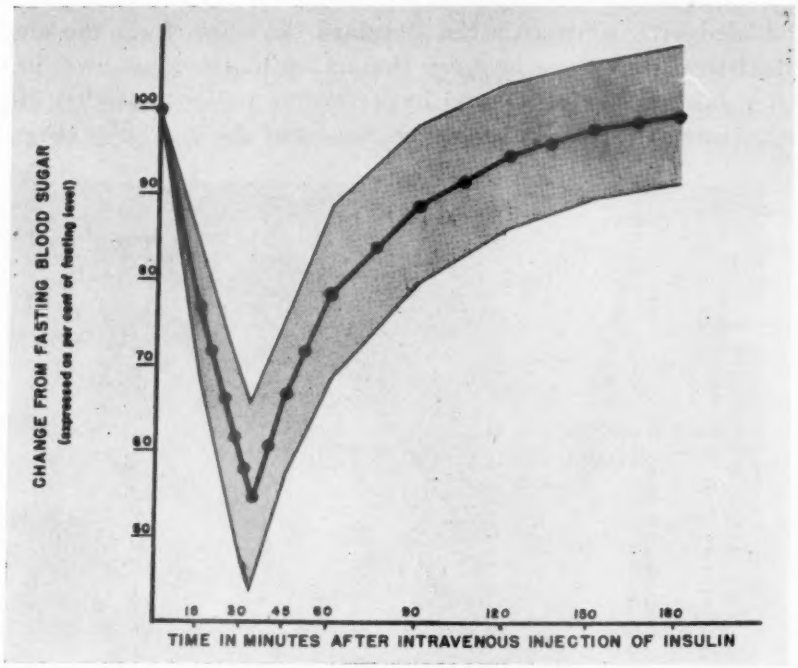

Fig. 1.—The composite insulin tolerance curve of 53 normotensive nondiabetic patients. Each point represents the mean and the shaded area represents the standard deviation from the mean. Values are expressed as per cent of the fasting level.

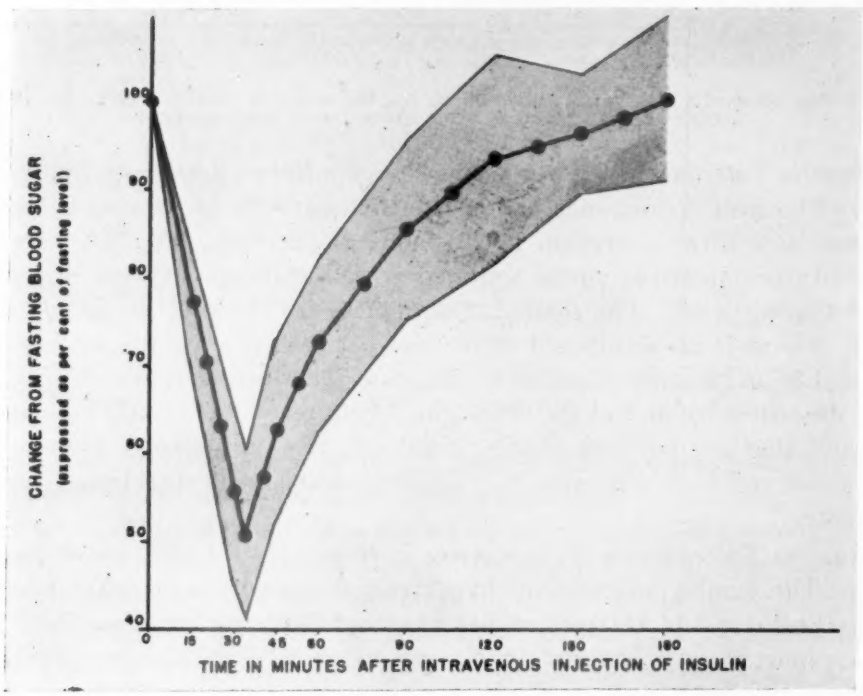

Fig. 2.—The composite insulin tolerance curve of 26 hypertensive patients studied before lumbodorsal sympathectomy. The values are plotted as in Fig. 1.

excluded. The results are shown in Fig. 1, in which the dots represent means and the shaded area represents the standard deviation from the mean. There was no statistical difference between thefasting blood sugar level in normotensive (90.3 ± 7.5 mg. per cent) and hypertensive patients (86.9 ± 10.5 mg. per cent), or between the insulin tolerance curves of the 2 groups (Figs. 1 and 2).

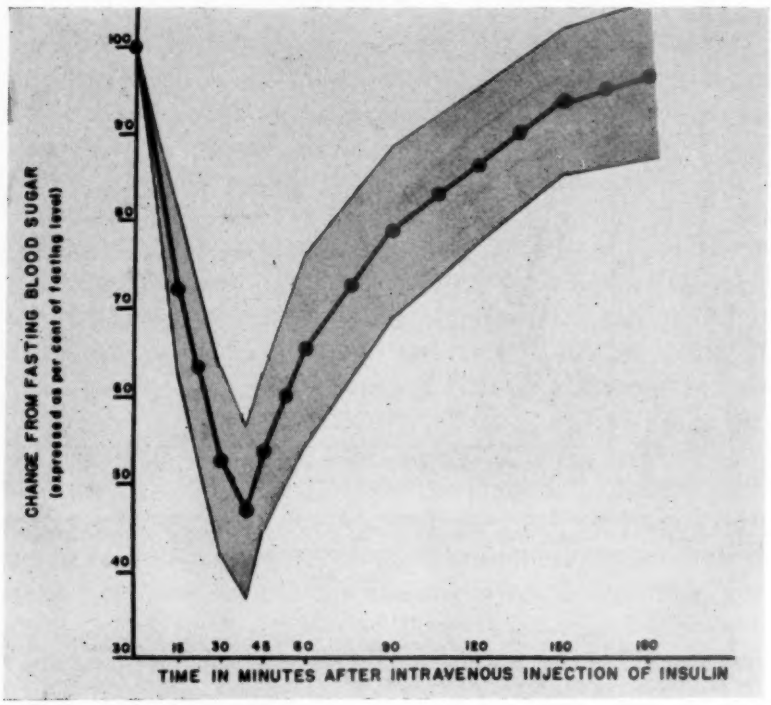

Fig. 3.—The composite insulin tolerance curve for the same 26 patients as in Fig. 2, but late (average 14.5 months) after lumbodorsal sympathectomy.

Insulin Tolerance in Hypertensive Patients Before Lumbodorsal Sympathectomy.—The insulin tolerance of hypertensive patients was tested before operation and late after operation in 26 identical patients. Fig. 2 represents the composite preoperative curve obtained with the means expressed as per cent of the fasting level. The shaded area depicts the standard deviation from the mean. There is no significant difference between this insulin tolerance curve and that of normotensive patients (Fig. 1). The insulin-resistant hypertensive cases described by de Takats[4] were not encountered. It should be emphasized, however, that the patients studied here were not unselected. They comprised only those patients who were not diabetic and had been selected for sympathectomy.

Insulin Tolerance in Hypertensive Patients After Lumbodorsal Sympathectomy.—The insulin tolerance of hypertensive patients early after lumbodorsal sympathectomy and between stages of sympathectomy was described in a previous report.[25] Approximately a year after sympathectomy (average 14.5 months), the decreased sensitivity found early after operation was no longer present and, in fact, there was a demonstrable, significantly increased sensi-

tivity to insulin (Fig. 3). Insulin tolerance curves in 26 identical patients before and after lumbodorsal sympathectomy are shown in Fig. 4. It is clear that the increased resistance acquired early after operation is lost. When compared with the preoperative curve, the values late after operation show a significantly greater maximum fall and a significantly delayed recovery from the hypoglycemia.

In 18 of the 26 patients tested late after operation, the denervation extended to and included the second lumbar ganglion or lower. In 8, the denervation extended only to and including the first lumbar ganglion or above. Analysis of the insulin tolerance curves obtained from these 2 groups showed no significant differences between them.

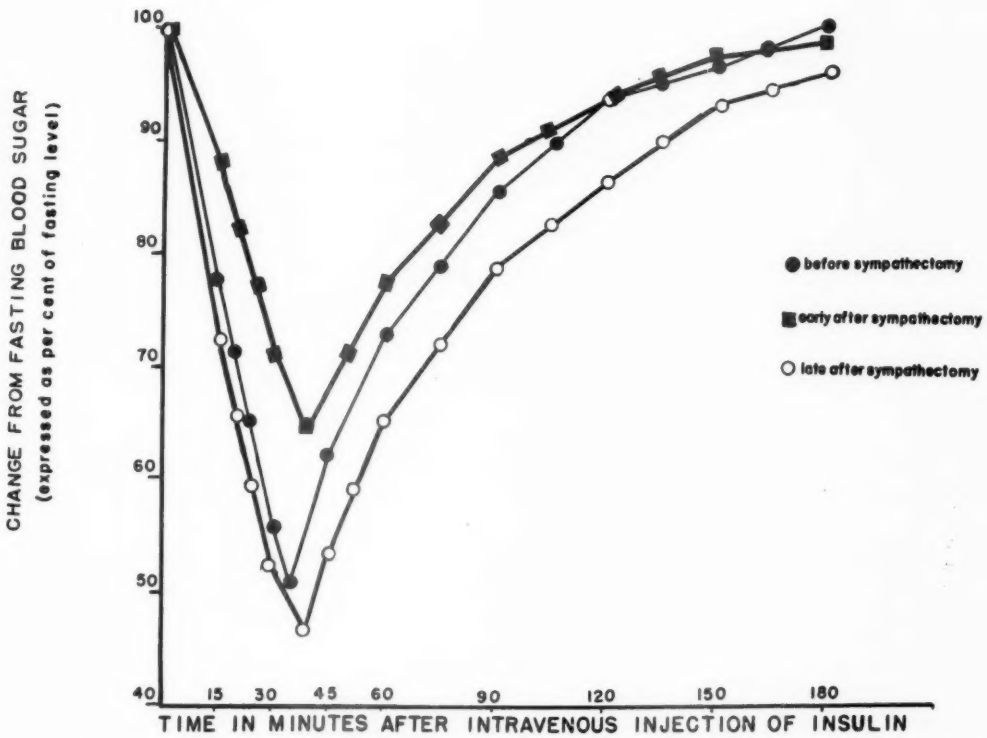

Fig. 4.—The composite insulin tolerance curves for the identical 26 patients before and late after lumbodorsal sympathectomy and for 20 of these same patients for whom curves had been determined early (average 10.7 days) after sympathectomy.

Three patients did show a decidedly greater sensitivity to insulin than the other 23 patients in the group. Their curves are represented in Fig. 5. One of the patients (C. B., indicated by squares) actually developed a convulsion following the intravenous administration of 0.08 unit of insulin per kilogram of body weight. Similar doses before operation and in the interim between stages of operation had shown normal insulin tolerance and increased insulin tolerance respectively. Patient D. D. (indicated by dots), when tested 1 year after operation, showed remarkable resistance to hypoglycemia in that even after 3 hours from the time of insulin injection, the blood sugar concentration was

still 39 mg. per cent below the fasting level. The rate of drop of the blood sugar was slightly less than that of the other 2, and she showed no tendency toward convulsions. Patient F. W. (indicated by open circles) showed a greater sensitivity to insulin 1 year after operation than preoperatively, and more so than the average of the other patients studied. The blood sugar dropped 57 mg. from the fasting concentration, or to 36 per cent of the fasting level. She became very weak and hungry during the test, but there were no convulsions. The late postoperative tests were repeated a second time in patients D. D. and F. W. with almost identical curves.

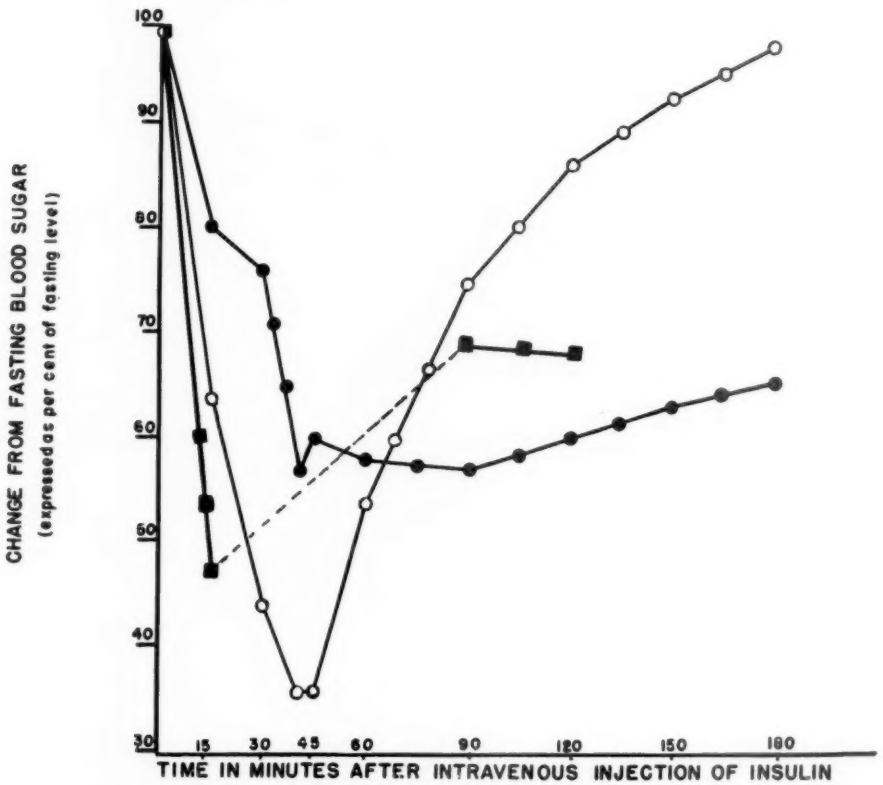

Fig. 5.—The insulin tolerance curves of 3 patients (D. D., dots; F. W., open circles; C. B., squares) who showed unusual sensitivity to insulin late after lumbodorsal sympathectomy for hypertension. All 3 were women.

Incidence of Different Degrees of Hypoglycemia Before and After Sympathectomy.—In the earlier report,[25] it had been observed that greater degrees of hypoglycemia occurred before sympathectomy than shortly afterward. A comparison of the results before sympathectomy with those about 1 year later (average 14.5 months) shows a greater incidence of severer degrees of hypoglycemia late after operation than before operation (Fig. 6). The chart (Fig. 6) shows that late after operation 4 of the 26 patients developed hypoglycemia of 35 per cent of the fasting values, while none of the patients developed this degree of hypoglycemia before sympathectomy or early after the operation. Late after operation 7 of the 26 patients developed hypoglycemia to 40 per cent, or lower, of the fasting levels.

Bromsulfalein Excretion

Bromsulfalein Retention in Patients With Hypertension.—The test was done in 61 patients, 23 male and 38 female, for whom sympathectomy was recommended. Their average age was 42 years. The mean retention for this group was 3.7 per cent of the injected dose with a standard error of 0.5. Between stages of operation, the retention was 8.1 per cent with a standard error of 1.3 in 25 patients. During the early postoperative period, the test was done in 36 patients. The mean retention was 7.4 per cent with a standard error of 1.0. Approximately one year (average 15.2 months) postoperatively, in 14 patients, the mean retention was 5.1 per cent with a standard error of 2.1. With the exception of the periods between and shortly after operation, lumbodorsal sympathectomy had no statistically significant effect upon liver function as

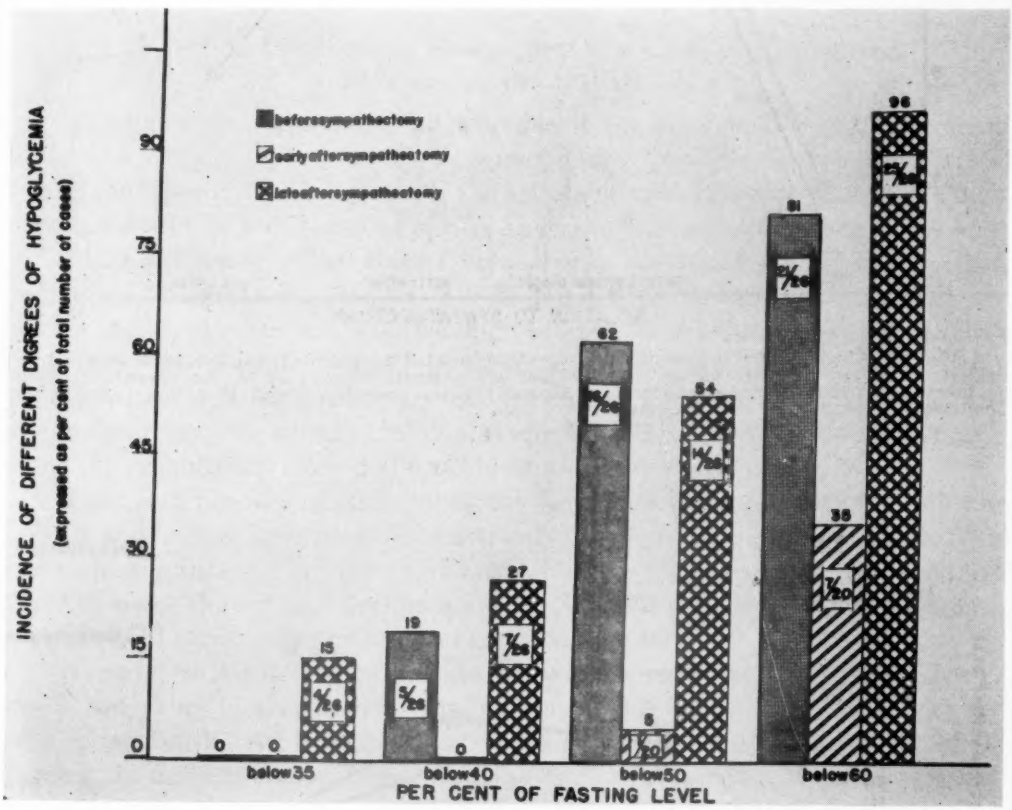

Fig. 6.—The incidence of different degrees of hypoglycemia before, early after, and late after lumbodorsal sympathectomy for hypertension. The decreased sensitivity to insulin early after operation and the increased sensitivity late after operation are obvious.

measured by bromsulfalein excretion. The increase in the mean retention demonstrable during the early postoperative period, 1 to 3 weeks after completion of lumbodorsal sympathectomy, is probably a nonspecific effect of the operation since as much change was found between stages of sympathectomy as after completion of the operation. These results are demonstrated in Fig. 7.

When only identical patients are considered comparable results are obtained. Twenty-two patients had both preoperative and interim determinations. Before operation, the average retention was 3.0 per cent with a stand-

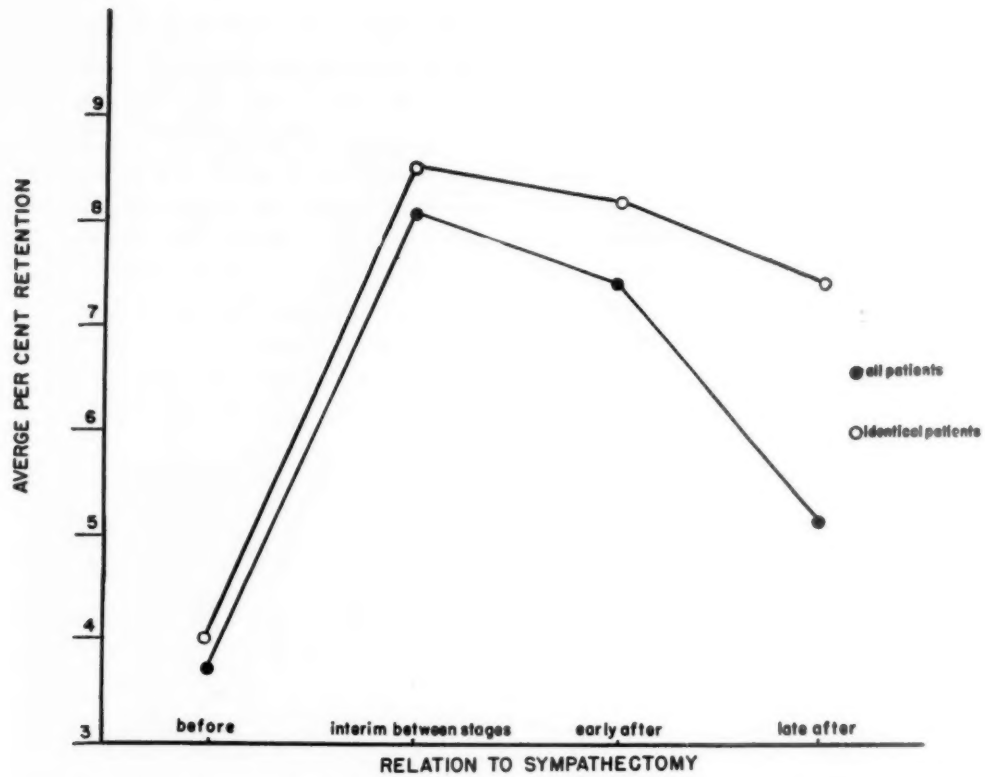

Fig. 7.—The average bromsulfalein retention related to lumbodorsal sympathectomy temporally. The dots are the means obtained for all patients tested; 61 before operation; 25 in the interim between stages of operation; 36 early after operation; and 14 a year later. The open circles represent 8 identical patients.

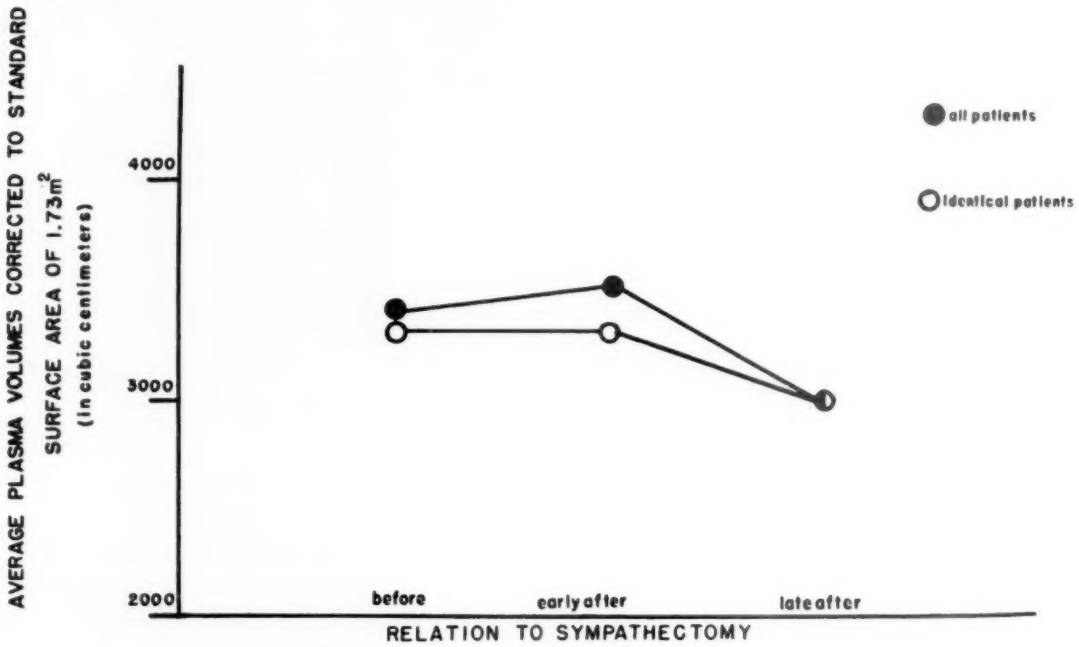

Fig. 8.—The mean plasma volumes for all patients studied (dots) and for 9 identical patients (open circles) related temporally to lumbodorsal sympathectomy.

ard error of 0.7 per cent. During the interim between stages of operation, the average retention was 7.9 per cent with a standard error of 1.5 in the same 22 patients. Thirty-four patients had determinations before operation and early afterward. The preoperative retention was 3.6 per cent, with a standard error of 0.6. In the same patients, the early postoperative retention was 7.3 per cent with a standard error of 1.0. Fourteen identical patients were tested preoperatively and 1 year postoperatively. The preoperative average was 2.8 per cent with a standard error of 1.0. In the same patients, 1 year after operation, the average retention was 5.1 per cent with a standard error of 2.1. The late postoperative findings do not differ significantly from the values observed before operation. The levels of bromsulfalein retention between stages of sympathectomy and early after completion of the operation were clearly elevated, suggesting a depression of this aspect of liver function.

Effect of Lumbodorsal Sympathectomy Upon the Blood and Thiocyanate Space Volumes

These studies were undertaken to see if the changes observed in animals after sympathectomy[15, 22] occur in hypertensive patients as well, and, if lasting changes are produced, to see if the effects of sympathectomy upon the blood pressure could be attributed to effects upon the fluid compartments of the body.

Plasma Volume.—The plasma volume was measured preoperatively in 55 patients. The mean volume was 3.39 L. per 1.73 square meters of surface area with a standard error of 0.07. During the early postoperative period (average 10.9 days) the plasma volume measured 3.54 L. with a standard error of 0.10 in 36 patients. In 15 patients 1 year (average 14.5 months) after lumbodorsal sympathectomy, the plasma volume averaged 3.01 L. with a standard error of 0.16. The results are recorded in Table I and illustrated in Fig. 8.

The mean plasma volume during the early postoperative period was higher than it was before operation. Statistically, however, this difference was found not to be significant. A year after operation, the plasma volume averaged over 375 c.c. lower than it was preoperatively. This difference was more than twice the standard error of the means and is probably significant.

Hematocrit Value.—The average hematocrit value in 55 hypertensive patients for whom lumbodorsal sympathectomy was recommended was 42 per cent with a standard deviation from the mean of 4.9 and a standard error of 0.7. During the early postoperative period (averaging 10.9 days), 36 patients showed hematocrit levels which averaged 39 per cent with a standard deviation of 4.8 and a standard error of 0.8. Late after sympathectomy (averaging 14.5 months), 15 patients had hematocrit values averaging 43 per cent with a standard deviation of 4.5 and a standard error of 1.2 (Table I). In the early postoperative period, there is a slight but significant fall of the hematocrit value. Late after operation, along with the contraction of the plasma volume, the hematocrit value has returned to the normal preoperative level.

Red Blood Cell Volume.—The red blood cell volume was determined preoperatively in 55 patients. The mean was 2.5 L. with a standard deviation of 0.63, and a standard error of 0.08. In the early postoperative period, it was

determined in 36 patients for whom the mean was 2.29 L., the standard deviation was 0.52, and the standard error was 0.09. There appears to be a drop in the red blood cell volume early after operation, but the decrease is just short of twice the standard error of the means and is of doubtful significance. Late after operation (average 14.5 months), the red blood cell volume was determined in 15 patients. The mean was 2.25 L. with a standard deviation of 0.49 and a standard error of 0.13. Here, too, the statistical significance of this fall in red cell volume late after operation was questionable.

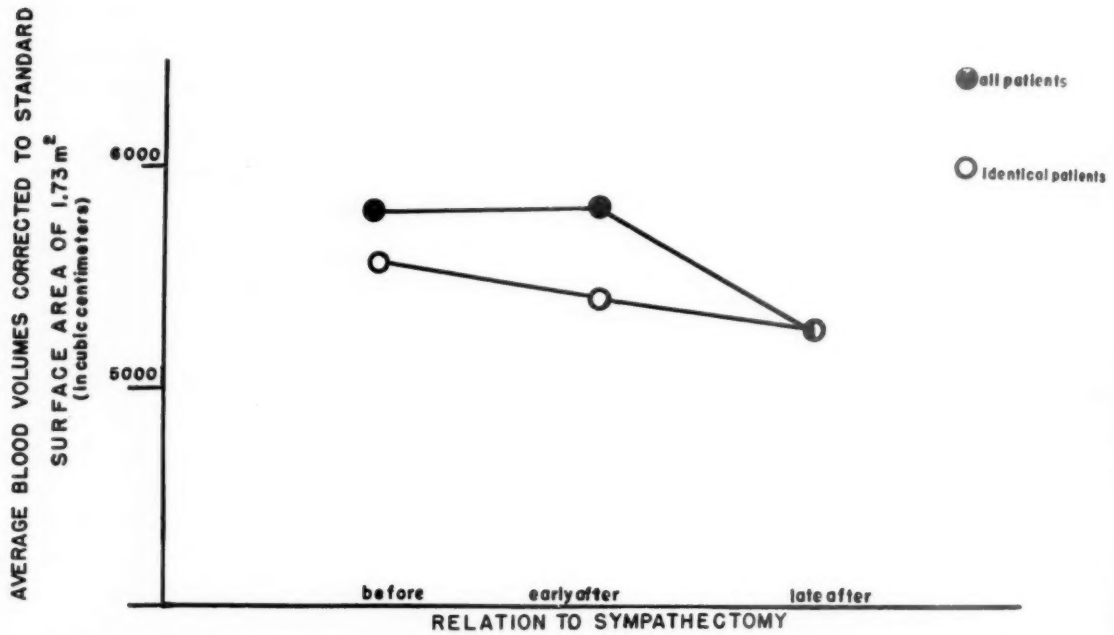

Fig. 9.—The mean total circulating blood volumes for all patients (dots) and for 9 identical patients (open circles) related temporally to lumbodorsal sympathectomy.

Total Blood Volume.—Preoperatively, the mean total circulating blood volume was found to be 5.85 liters with a standard error of 0.13 in 55 patients. This is a normal value. In the early postoperative period (averaging 10.9 days after completion of the operation) the total blood volume was 5.83 liters with a standard error of 0.14 in 36 patients. This represents no significant change in total volume. When measured 1 year postoperatively (average 14.5 months), the total circulating blood volume was 5.26 L. with a standard error of 0.25 in 15 patients. These results are recorded in Table I. When tested statistically there is no significant difference between preoperative and early postoperative values. The mean circulating blood volume is significantly lower 1 year after operation than it was preoperatively. The difference between the means is just over twice their standard error. The actual change is so small, however, that it is unlikely that important clinical effects of sympathectomy can be attributed to this change. While showing a similar trend in their total blood volumes, the number of identical patients studied in this manner is too small for statistical analysis.

Extravascular "Thiocyanate Space."—The extravascular thiocyanate space was determined before operation in 43 patients and corrected to standard sur-

face area of 1.73 square meters. The mean was 13.1 L. with a standard deviation of 2.35 from the mean and a standard error of 0.36. The mean represented 19.6 per cent of the body weight. The average value obtained during the early postoperative period in 28 patients was 15.3 L. with a standard deviation of 3.5 and a standard error of 0.66. This represented 23.8 per cent of the body weight. During the late postoperative period, the test was done in 15 patients. The mean extravascular thiocyanate volume was 12.4 L. with a standard deviation of 2.3 and a standard error of 0.60. This value represented 18.3 per cent

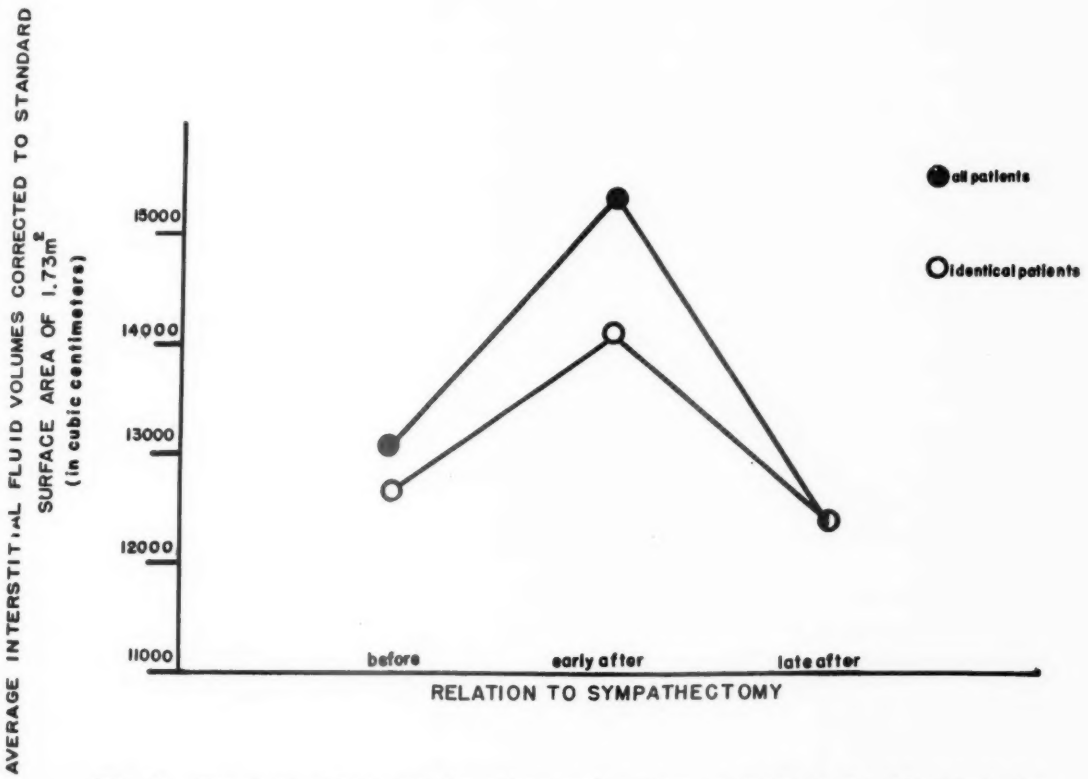

Fig. 10.—The mean volumes of the extravascular space available to the thiocyanate ion related temporally to lumbodorsal sympathectomy. The dots represent means for all patients studied; the open circles represent those for 9 identical patients. Although it is recognized that there is some diffusion of the ion into red blood cells, it is believed that the space approximates closely the interstitial fluid volume.

of the body weight. These results indicate that early after lumbodorsal sympathectomy there is a significant expansion of the extravascular space available to the thiocyanate ion and interpreted here as approximating the volume of interstitial fluid. The difference between the means was 3 times their standard error. This expansion disappears during the ensuing year, at the end of which time the average interstitial fluid volume was the same as it was before operation (Table I; Fig. 10).

Since it was thought possible that the expansion of the thiocyanate space observed during the early postoperative period may have been due to the administration of parenteral fluid during operation and immediately afterward, the relationship between the thiocyanate space volumes and the volume of

TABLE I. THE EFFECT OF LUMBODORSAL SYMPATHECTOMY UPON THE BLOOD, PLASMA AND THIOCYANATE SPACE VOLUMES

	BEFORE SYMPATHECTOMY						EARLY AFTER SYMPATHECTOMY						LATE AFTER SYMPATHECTOMY					
	ALL CASES (55* PATIENTS)			IDENTICAL CASES (9 PATIENTS)			ALL CASES (36* PATIENTS)			IDENTICAL CASES (9 PATIENTS)			ALL CASES (15 PATIENTS)			IDENTICAL CASES (9 PATIENTS)		
	MEAN	STANDARD DEVIATION	STANDARD ERROR	MEAN	STANDARD DEVIATION	STANDARD ERROR	MEAN	STANDARD DEVIATION	STANDARD ERROR	MEAN	STANDARD DEVIATION	STANDARD ERROR	MEAN	STANDARD DEVIATION	STANDARD ERROR	MEAN	STANDARD DEVIATION	STANDARD ERROR
Plasma volume (liters)	3.39	0.49	.07	3.3	0.58	0.16	3.54	0.59	0.1	3.3	0.69	.23	3.01	0.62	0.16	3.0	0.57	0.19
Hematocrit (per cent)	42.	4.9	0.7	41.	5.1	1.7	39.	4.8	0.8	39.	4.5	1.5	43.	4.5	1.2	43.	4.7	1.6
Red blood cell volume (liters)	2.5	0.63	.08	2.3	0.44	0.15	2.29	0.52	.09	2.16	0.61	0.20	2.25	0.49	0.13	2.2	0.40	0.13
Total circulating blood volume (liters)	5.85	0.98	0.13	5.57	3.4	1.1	5.83	0.82	0.14	5.44	1.2	0.4	5.26	0.97	0.25	5.28	0.78	0.26
Extravascular thiocyanate space (liters)	13.1	2.35	0.36	12.7	2.3	0.77	15.3	3.5	0.66	14.0	2.2	0.74	12.4	2.3	0.60	12.4	1.8	0.61

*In the case of thiocyanate space these total numbers were 43 and 36, respectively.

parenteral fluid administered was studied (both blood and crystalloids). There was no correlation and, while fluid balance studies were not done, it was believed that the expansion was due to a retention of water during the early postoperative period.

Effect of Lumbodorsal Sympathectomy Upon the Renal Blood Flow

The renal blood flow was studied in 11 patients both before and after lumbodorsal sympathectomy. The average findings before and after operation in this group of patients are recorded in Table II. None of the changes are significant when the data are grouped in this manner. It is important to observe, however, that when these 11 patients are classified according to the severity of their disease, they represent at least 3 different groups. They form a mixed population and should therefore not be treated as a uniform group. Unfortunately, the number of cases studied to date is too small to permit subgroups of sufficient size for statistical study, and the following data are presented for purposes of orientation rather than to establish proof of the ideas suggested.

TABLE II. MANNITOL AND HIPPURATE CLEARANCES IN ELEVEN PATIENTS BEFORE AND AFTER LUMBODORSAL SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

	AVERAGE RATE OF GLOMERULAR FILTRATION (C.C. PER MINUTE) (CM)	AVERAGE TOTAL EFFECTIVE RENAL PLASMA FLOW (C.C. PER MINUTE) (CPAH)	AVERAGE MAXIMAL TUBULAR EXCRETORY MASS (MG. PAH PER MINUTE) (TM)	AVERAGE FILTRATION FRACTION (CM/CPAH)
Preoperative	83	398	61	0.22
Postoperative	76	430	50	0.20

Correlation With Degree of Pathologic Change in the Kidneys.—Histologic examination of the kidneys was done in only 6 of these 11 patients. The specimens were examined by the department of pathology and graded according to principles already described (Talbott and associates).[29] The 6 patients fell into 3 groups of 2 each, showing pathologic changes in the kidneys described as grades 2, 3, and 4. The 2 patients with grade 4 changes in the kidney had been classified clinically as "malignant hypertension." The results of the renal clearances are recorded in Table III.

It is apparent that in the mildest of the 3 groups, the rate of glomerular filtration and the renal plasma flow were within normal limits. The filtration fraction was high. Lumbodorsal sympathectomy caused a slight drop in the rate of glomerular filtration, a rise in the effective renal plasma flow, a drop in the filtration fraction, and no significant change in the hippurate-TM. In the severest group, the rate of glomerular filtration and the effective renal plasma flow were less than one-half their normal values. The hippurate-TM was low. The operation caused no change in the rate of glomerular filtration or in the hippurate-TM but was followed by a decrease in the effective renal plasma flow, and an increase in the filtration fraction. The 2 patients with grade 3 changes in the kidneys showed a fall in the glomerular filtration rate after operation, opposite effects upon the total renal plasma flow, no change or a drop in the hippurate-TM, and a distinct fall in the filtration fraction.

TABLE III. MANNITOL AND HIPPURATE CLEARANCES IN HYPERTENSIVE PATIENTS BEFORE AND AFTER LUMBODORSAL SYMPATHECTOMY IN RELATION TO DEGREE OF HISTOLOGIC CHANGE IN KIDNEYS

CASE NO.	DEGREE OF HISTOLOGIC CHANGE IN KIDNEYS (GRADE)	DEGREE OF OPHTHALMOSCOPIC CHANGE		RATE OF GLOMERULAR FILTRATION (C.C. PER MINUTE) (CM)		TOTAL EFFECTIVE RENAL PLASMA FLOW (C.C. PER MINUTE) (CPAH)		MAXIMAL TUBULAR EXCRETORY CAPACITY (MG. PAH PER MINUTE) (TM)		FILTRATION FRACTION (CM/CPAH)	
		HYPERTENSIVE (GRADE)	ARTERIOSCLEROTIC (GRADE)	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE
1	2	4	0	138	120	506	680	80	92	0.27	0.18
2	2	0	0	117	95	585	780	85	73	0.20	0.12
3	3	0	0	64	42	281	372	46	31	0.22	0.13
4	3	2-3	0	121	78	590	525	89	59	0.20	0.11
5	4	3	3	62	69	232	200	42	35	0.27	0.34
6	4	3	2	48	51	183	156	28	28	0.26	0.33

It would appear that in patients with relatively less severe changes in the kidneys, the glomerular filtration rate and fraction are both decreased by lumbodorsal sympathectomy. In the group with severe changes in the kidneys, there is no effect upon the rate of glomerular filtration, but the total renal plasma flow falls and the filtration fraction consequently rises.

Correlation With the Two-Hour Excretion of Phenolsulfonephthalein.—Nine of the 11 patients studied had preoperative determinations of the phenolsulfonephthalein excretion. These were divided empirically into 2 groups: one of 3 patients whose phenolsulfonephthalein excretion was below 60 per cent in 2 hours, and the other of 6 patients whose excretion was 60 per cent or over. The effects of operation upon the renal clearances in these 2 groups are shown in Table IV. The phenolsulfonephthalein excretions are all preoperative values. It is apparent that patients with the better phenolsulfonephthalein excretion had better clearances, but the filtration fractions in the 2 groups were about the same. Conclusions with certainty here are not possible because of the small numbers of cases, but the data do suggest that renal changes resulting in a high filtration fraction are the early manifestations of hypertension in the kidneys and serious impairment of both glomerular filtration and renal plasma flow follow later.

TABLE IV. MANNITOL AND HIPPURATE CLEARANCES IN HYPERTENSIVE PATIENTS BEFORE AND AFTER LUMBODORSAL SYMPATHECTOMY AND RELATED TO THE TWO-HOUR EXCRETION OF PHENOLSULFONEPHTHALEIN INJECTED INTRAVENOUSLY

	PHENOLSULFONEPHTHALEIN EXCRETION (AS PER CENT EXCRETED AFTER 2 HOURS)			
	35 TO 60 (3 PATIENTS)		60 TO 85 (6 PATIENTS)	
AVERAGE CLEARANCES	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE
Glomerular filtration rate (CM) (c.c. per minute)	61	66	99	79
Renal plasma flow (CPAH) (c.c. per minute)	266	273	478	490
Maximal tubular excretory mass (TM) (mg. PAH per minute)	46	35	70	55
Filtration fraction (CM/CPAH)	0.24	0.27	0.22	0.18

Correlation With the Effect of Lumbodorsal Sympathectomy Upon the Blood Pressure.—Only 9 patients are available who have been followed for 1 year or more after determination of the renal blood flow. They are divided into 2 groups: 5 patients who were improved as far as the blood pressure was concerned (preoperative blood pressure averaged 202/123; postoperative blood pressure averaged 124/87) and 4 patients who were not improved in this regard (preoperative blood pressure averaged 192/120; postoperative blood pressure averaged 215/132). The blood pressure was considered improved when the diastolic pressure fell 40 mm. of mercury from the preoperative level or fell below 90 mm. of mercury as an absolute value.

The glomerular filtration rate: The rate of glomerular filtration was nearly normal preoperatively in the patients who improved after operation. It was

low in the patients who did not improve after operation (Table V). After operation, the rate of glomerular filtration dropped (23 per cent) in the group that had a high rate preoperatively and rose slightly (9 per cent) in the 4 patients who had a low rate preoperatively and were not improved by operation (Table V).

TABLE V. MANNITOL AND HIPPURATE CLEARANCES IN HYPERTENSIVE PATIENTS BEFORE AND AFTER LUMBODORSAL SYMPATHECTOMY RELATED TO THE EFFECT OF OPERATION UPON THE BLOOD PRESSURE

AVERAGE CLEARANCES	BLOOD PRESSURE IMPROVED BY SYMPATHECTOMY (5 PATIENTS)		BLOOD PRESSURE NOT IMPROVED BY SYMPATHECTOMY (4 PATIENTS)	
	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE
Glomerular filtration rate (CM) (c.c. per minute)	109	84	62	68
Renal plasma flow (CPAH) (c.c. per minute)	536	557	314	345
Maximal tubular excretory capacity (TM) (mg. PAH per minute)	78	60	49	44
Filtration fraction (CM/CPAH)	0.21	0.15	0.21	0.22

The renal plasma flow: The average renal plasma flow was within the limits of normal for the 5 patients who were improved by operation and was not affected appreciably by the sympathectomy. The 4 per cent rise was not thought significant. In the 4 patients who were not improved by sympathectomy it was only about one-half the normal value preoperatively. This group showed a 10 per cent increase in the renal plasma flow after operation, but, as for the patients who improved, this is of doubtful significance (Table V).

The total renal excretory mass (hippurate-TM): The maximal capacity of the kidneys to excrete sodium para-aminohippurate (TM) in the patients who were improved by lumbodorsal sympathectomy was normal (Table V). Among those who were not improved by sympathectomy, the TM was only about one-half the normal value. Sympathectomy produced a drop in the hippurate-TM for both groups. The average hippurate concentration in the serum during these determinations was 90 mg. per cent. The drop in the hippurate-TM following sympathectomy is difficult to explain. It could represent a change in the efficiency of the kidneys for extracting the hippurate from the blood flowing through them.

The filtration fraction: The average filtration fraction (Table V) was higher than the normal filtration fraction of 0.19 to 0.20 (Goldring and Chasis[13]) for both the patients who improved after sympathectomy and for those who did not. After operation, the filtration fraction fell for the group which improved, but did not change or rose still higher for the cases which did not improve.

The ratio of rate of glomerular filtration to maximal tubular excretory mass (normal 1.7): Among the patients who experienced a lowering of the blood pressure after sympathetcomy, the average ratio was 1.4. Among those who did

not improve, the average ratio was 1.3. After operation, the ratio was 1.2 for those who improved and 1.6 for those who do not improve. The low ratios in these cases were unexpected.

The ratio of renal plasma flow to maximal tubular excretory mass (normal 9.2): This value was 6.8 preoperatively for the patients whose blood pressure dropped after sympathectomy. It was 6.5 preoperatively for the patients whose blood pressure did not drop after operation. Postoperatively, the ratio was 9.6 for those who improved, and 7.6 for those who did not improve. These figures suggest an improvement in the total renal circulation relative to functional renal elements after operation, and more so for those who improved than for those who did not.

DISCUSSION

An increased tolerance for insulin early after lumbodorsal sympathectomy and splanchnicectomy has already been reported.[25] This was an unexpected finding, in view of numerous previous investigators' experiences with animals. The results reported here indicate that late after sympathectomy, subjects were clearly more sensitive to insulin and slower in recovering from the hypoglycemia induced by it, but, for the group as a whole, the decreased tolerance for insulin was not nearly as great as that observed in animals. Three patients did have marked sensitivity to insulin, and, indeed, 1 of them experienced a convulsion following the administration of insulin. The preoperative and early postoperative responses in these 3 patients had not been outstanding and the extent of sympathectomy had been no greater than for the average of the group. In fact, 1 of the patients (F. W.) had had only a supradiaphragmatic sympathectomy and splanchnicectomy extending from the ninth through the twelfth thoracic ganglia bilaterally.

The responses of the individual patients were studied in various combinations to see if there was any relationship between the extent of sympathectomy and the sensitivity to insulin. None was found. It appears that resection of the splanchnic nerves is the important feature as far as sensitivity to insulin is concerned.

The difference between man and animals in this regard is difficult to explain. The finding suggests that homeostasis of blood sugar in man is accomplished by important mechanisms in addition to the adrenal medulla and its immediate nerve supply. In man, the insulin tolerance cannot be used as a reliable test for completeness or persistence of sympathetic denervation of the splanchnic area. The late sensitivity to insulin acquired by denervation of the splanchnic area is not sufficient to be discriminative in individual cases.

Bromsulfalein is cleared from the blood almost entirely by the parenchymal cells of the liver.[19] Variations in this clearance might arise from changes in the rate of blood flow through the liver or in the ability of the liver cells to extract the bromsulfalein from the blood passing through it. The results of this study suggest that the bromsulfalein clearance is depressed by lumbodorsal sympathectomy during the early postoperative period and returns to the normal preoperative value late after operation. The fact that the depression

occurs and is just as great after only the first stage of a two-stage sympathectomy, would indicate that the effect is very likely a nonspecific one of the operation.

In a careful study of the rate of disappearance of the drug under various conditions, Mendeloff and co-workers[19] found that, in 10 cases, the rate of clearance was generally, but not invariably, decreased after lumbodorsal sympathectomy. Wilkins and associates[31] reported an increase in the rate of blood flow through the liver early after lumbodorsal sympathectomy for hypertension. Their finding makes it unlikely that the fall in the bromsulfalein clearance described in this report is due to a decrease in the rate of blood flow through the liver and raises the possibility that operation affected the ability of the liver to extract the substance from the blood flowing through it.

The data concerning changes in blood and plasma volume are noteworthy because of their relative constancy before and after sympathectomy. The slight contraction of the plasma volume late after operation was thought to be of little importance. The expansion of the plasma volume which has been observed in cats[15] and the contraction of the red blood cell volume observed in dogs[22] after sympathectomy has not been found in man after lumbodorsal sympathectomy for hypertension. The reduction in the total blood volume reported early after operation by Freis and Smithwick[11] was not observed. Minor changes which did appear are not significant when tested statistically. While the hematocrit value did decrease significantly after sympathectomy, this change was accompanied by sufficient change in the plasma volume so that the circulating red blood cell volume remained within normal limits. What did occur after sympathectomy in the patients discussed in this report was a striking expansion of the extravascular thiocyanate space. This confirms the observations of Schafer[22] in dogs and of Freis and Smithwick[11] in man. Again, it is doubtful that this expansion of the thiocyanate space is a specific effect of sympathectomy. It has been observed after major surgical procedures other than lumbodorsal sympathectomy[18, 28] and is therefore probably a nonspecific result. The effects of the operations upon the extravascular thiocyanate space showed no correlation with the volume of blood and crystalloids which the patients received in the operating room or during the early postoperative period. It should be noted, however, that detailed studies of water and electrolyte balance were not done. A normal daily urinary output was taken to imply adequate hydration.

Late after sympathectomy, the increased volume of the extravascular thiocyanate space observed early after operation returned to within the limits of the preoperative value. These data support the conclusion of Freis and Smithwick[11] that whatever the effects which lumbodorsal sympathectomy may have upon the blood pressure of hypertensive patients, the effects are probably not a reflection of changes in the fluid compartments of the body.

The data recorded in Table I would indicate that lumbodorsal sympathectomy has no significant effect upon the glomerular filtration, the effective renal plasma flow, and the maximal capacity of the kidneys to excrete sodium paraaminohippurate. This would agree, in general, with the reports of Alving and

co-workers[1]; Corcoran and Page[3]; Findley, Clinton, and Edwards[7]; Foa and associates[8, 9, 10]; Goldring and Chasis[13]; Selzer and Friedman[24]; and Talbott and associates.[29] It must be recalled, however, that any group of hypertensive patients is likely to be composed of a number of different categories differing from each other in severity of pathologic change and possibly in etiology as well. If the cases are segregated into different classes a suggestion of order begins to appear (Table III).

When the results of studies of the mannitol and sodium para-aminohippurate clearances are qualified by the effectiveness of the operation in reducing the blood pressure after 1 year, a clear relationship appears among the 9 patients studied in this manner (Table V). Those patients who improved had rates of glomerular filtration and of effective renal plasma flow which were within normal limits. Those who demonstrated no effect of sympathectomy upon the blood pressure showed markedly diminished values. The same trend was observed when the results of operation were correlated with the 15 minute and the 2 hour excretion of phenolsulfonephthalein injected intravenously (Table IV). The filtration fraction was high preoperatively in both groups of patients. It fell in those who improved and not in those who failed to improve. It seems that a high filtration fraction appears early in essential hypertension and becomes irreversible late.

Foa and associates[10] concluded that while they could demonstrate no improvement in the renal circulation after supradiaphragmatic splanchnicectomy, in view of the fact that postoperative determinations were done at lower blood pressures, their figures actually represent a decrease in the resistance of the renal circulation. It is noteworthy, in this regard, that Selkurt, Hall, and Spencer[23] observed that until pressures of about 100 mm. of mercury are reached, the renal clearances are not affected appreciably by lowering the blood pressure even without denervation.

It is generally accepted by even the most critical that there is a small proportion of hypertensive patients who are benefited by lumbodorsal sympathectomy. Techniques for selecting this small group among the many have not been satisfactory. It is reasonable to expect that determination of the rate of glomerular filtration, the renal blood or plasma flow, and the maximal tubular excretory capacity may serve as useful tests for selection.

CONCLUSIONS

1. The physiologic effects of lumbodorsal sympathectomy in hypertensive patients other than upon the blood pressure are surprisingly few.

2. There is an increased sensitivity to insulin late after sympathectomy (Fig. 4) but not nearly as dramatic as that reported in the past for animals.

3. The volume of circulating red blood cells is not significantly affected by lumbodorsal sympathectomy. There is a drop in the hematocrit value early after operation with return to normal later, but the total red blood cell volume remains within the preoperative limits because of associated changes in the plasma volume (Table I).

4. The total blood volume and the plasma volume are found slightly decreased late after lumbodorsal sympathectomy, but the changes are not large enough to warrant attributing to them the effects of sympathectomy upon the blood pressure (Table I).

5. The extravascular thiocyanate space is increased early after sympathectomy and returns to normal late after sympathectomy. This is interpreted as a nonspecific effect of operation (Table I, Fig. 10).

6. The ability of the kidneys to clear the blood of mannitol and sodium para-aminohippurate is nearly normal in patients whose hypertension is only moderately severe. It is severely impaired in patients with severe hypertension (Table III).

7. A close correlation exists between the degree of histologic change in the kidneys and their ability to excrete mannitol and sodium para-aminohippurate (Table III).

8. Patients whose blood pressures were improved 1 year after sympathectomy had nearly normal renal clearances; those who were not improved by sympathectomy showed preoperative values which were nearly one-half the normal (Table V).

9. The filtration fraction was elevated both in the patients whose blood pressures improved after sympathectomy and those whose blood pressures were not affected. Among the former, however, the filtration fraction was decreased by sympathectomy; among the latter, the filtration fraction remained unchanged or increased (Table V).

10. The data presented in this report suggest that, in hypertensive patients with marked impairment of the rate of glomerular filtration and renal plasma flow, lumbodorsal sympathectomy does not produce a lowering of the blood pressure. A high filtration fraction, per se, however, does not preclude a favorable result.

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DISCUSSION

DR. K. S. GRIMSON.—I would like to congratulate Dr. Simeone on his excellent studies. May I ask whether the renal blood flow measurements were recent or late following operation? Similar tests before, early, and late after near-total transthoracic paravertebral sympathectomies revealed no indication of aid in prognosis. This operation, however, is more extensive than the lumbodorsal sympathectomy. As a matter of fact, unless

this renal function test proves satisfactory after further study we have no good method for predicting the effects of sympathectomy on blood pressure.

Late results of splanchnicectomy for hypertension are by and large relatively poor. As a result of our own studies and clinical observations, I am convinced that denervation of the abdominal viscera and the lower one-half or two-thirds of the body as done by lumbodorsal sympathectomy is inadequate. The near-total transthoracic sympathectomy which includes the heart, lungs, head, arms, and upper trunk as well as the abdominal viscera and lower trunk yields improved results. Using this more extensive sympathectomy one can get away from operating upon patients early in their hypertensive disease process and go into operation at a later stage when help is really needed. Mortality risk is minimum even at this later stage. The few operative deaths that occurred have been attributable to existing disease of the heart, kidney, or cerebral vessels rather than to technique or complication of sympathectomy.

I would like to ask for Dr. Simeone's comment on recommendation for extension of the area of sympathectomy to include the upper one-half of the body.

DR. F. A. SIMEONE (Closing).—These studies of the renal blood flow were done during the early postoperative period approximately 3 weeks after operation. We have not attempted to call these patients back after a year or so, because in an earlier study which Talbott, Castleman, Smithwick, Melville, and Pecora, published in 1943, it was shown that while early changes of minor degree do occur after sympathectomy, they were no longer demonstrable by the end of a year after operation.

Evelyn, Alexander, and Cooper studied the effects of sympathectomy upon the blood pressure and published some of their observations a year ago. They observed that in the group of patients they studied it did not seem to matter a great deal how extensive the paravertebral ganglionectomy was made in addition to the splanchnic resection. In other words, those who had had a relatively limited sympathectomy, as described by Peet, seemed to fare about as well as those who had even the most extensive of Dr. Smithwick's lumbodorsal sympathectomies.

Some of these patients had sympathectomies up to and including the second thoracic ganglion, but none of them was as extensive as Dr. Grimson's operation.

VENOUS ADAPTATION FOLLOWING BILATERAL RADICAL NECK DISSECTION WITH EXCISION OF THE JUGULAR VEINS

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THE venous system exhibits a remarkable ability to compensate for obstruction to its major channels.[1] Such an adaptation occurs after bilateral excision of the jugular system of veins. From a physiologic standpoint this procedure might be said to produce a "permanent Queckenstedt test." Immediate venous stasis with increased distal venous and cerebrospinal fluid pressure might be expected. Increased intracranial pressure might be anticipated. Evidences of decompensation of the extracranial circulation such as edema, cyanosis, and dilatation of the superficial veins might also be reasonably expected. Some of these changes do occur following bilateral removal of the jugular veins. The severity and permanency of such changes, however, are conditioned by the number and size of existing anastomoses and collaterals, the increased capacity of the venous bed under sustained increased pressure, and flow of blood through previously little used vessels.[2] To a certain degree, too, the extracranial and cervical lymphatics must serve to return increased amounts of fluid from the interstitial spaces (Fig. 1).

The venous system of the head is a complex network consisting of intracranial, extracranial, and interosseous divisions. Communications are abundant, the venous pressure is low, and reversal of flow easily occurs. The intracranial and extracranial portions communicate freely through the emissary and diploic veins, the large venous plexuses on both sides of the skull base, the veins of the orbit, and the veins of the neural and arterial foramina (Fig. 2).

The jugular bulbs are direct extensions of the lateral dural venous sinuses and are the largest channels for venous outflow from the cranial cavity. The dural venous sinuses do not always communicate at the confluence of the sinuses. Three vessel patterns[3] are described at this site: (1) The superior longitudinal sinus continues as the left or the right transverse sinus, usually the right. The straight sinus flows to the opposite side. (2) The superior longitudinal sinus divides and is distributed about equally to the right and left transverse sinuses. (3) There is a true confluence of the several sinuses. The straight sinus conveys blood from the lateral ventricles and the choroid plexuses while the longitudinal sinus drains the cerebral cortex. It is conceivable that if there are inadequate communications between the superior longitudinal sinus and the straight sinus and/or inadequate communications between the intracranial and the extracranial veins, severe degrees of stasis may result from interruption of only one internal jugular vein.

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In addition to the internal and external jugular veins, other channels through the neck are: the collecting veins of the posterior cervical region, the occipital, the profunda cervical, the posterior jugular, and the vertebral; the pharyngeal, pterygoid and the esophageal plexuses; and the vertebral venous plexus.

Although the vertebral, or rachidian, veins have been recognized by anatomists for over a century, their physiologic and clinical importance has only recently been emphasized.[4] This complex intercommunicating system of veins extends from the cranium to the coccyx (Fig. 3). Normally the vertebral veins are not of great physiologic importance but following venous obstruction they become a major by-pass. The vertebral venous system is composed of the internal vertebral plexus, the external vertebral plexus, and the communicating

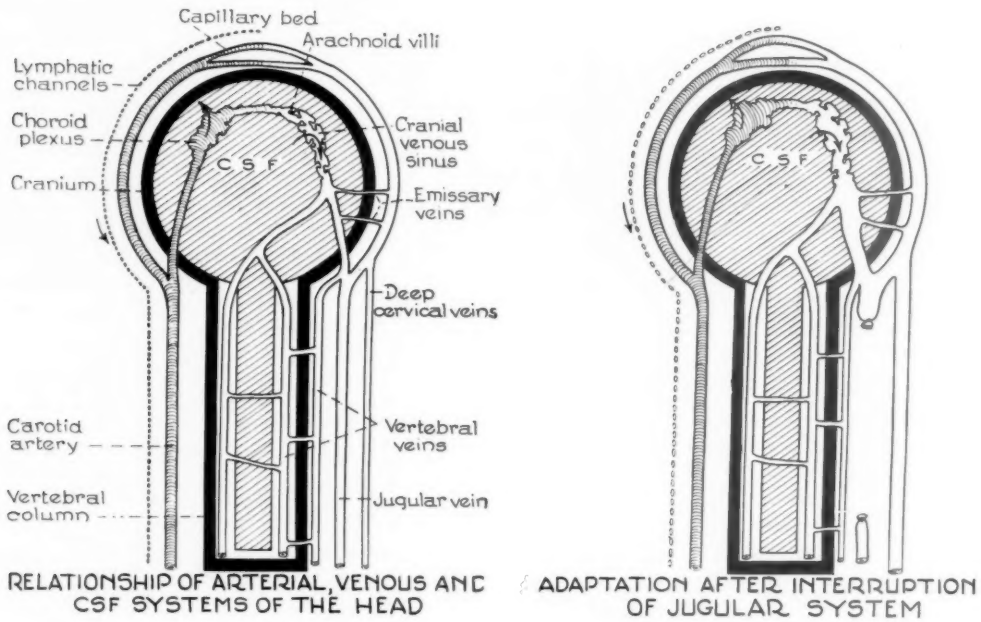

Fig. 1.—*A*, The fluid exchange mechanisms of the head are depicted diagrammatically. *B*, Changes incident to removal of the jugular veins depicted by increased size of the intracranial, extracranial and remaining cervical veins.

veins.[5] The entire system is united by many small irregular channels, and at each vertebral space the vertebral veins are in communication with the intracavitary veins of the thorax and abdomen, the intercostal veins, and other veins of the body wall. In the neck there are many anastomoses with veins of the neck viscera and the shoulder girdle. Batson[3] stated that although the total cross-sectional area of this system as it leaves the cranium has not been estimated it appears to exceed that of the two jugulars. It is probable, therefore, that the vertebral venous plexus is sufficient to provide for the entire drainage of blood from the cranial cavity.

Reports of bilateral jugular interruption are meager and most are found in otolaryngological journals. Evans (1942)[6] reviewed the subject and reported a case of bilateral jugular ligation for acute bilateral suppurative mas-

toiditis with recovery. Of seven cases reported by general surgeons, three of the patients died, three recovered, and the end result in one was unknown. Deaths of two patients occurred almost immediately after ligation of the second jugular. In these cases the second stage of the operation was done sixteen days and one month after the first stage. In each instance it appeared that death could be attributed to interference with cerebral blood flow.

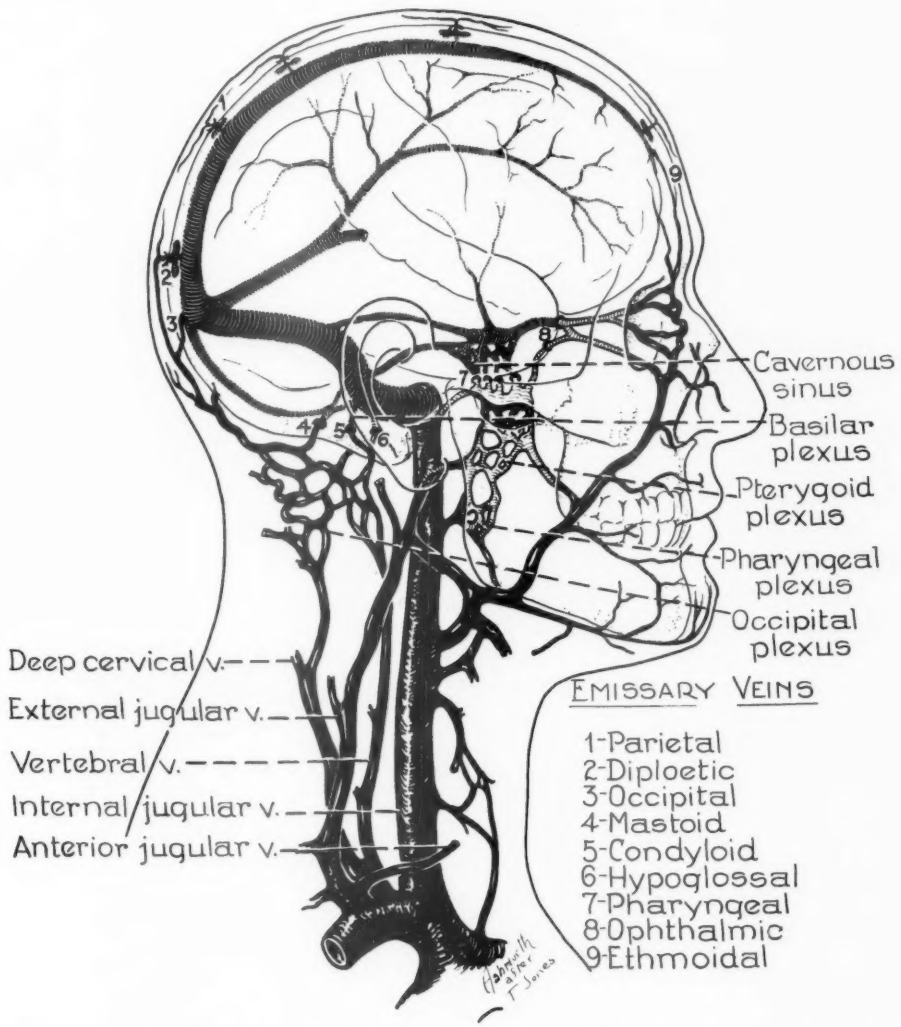

Fig. 2.—The venous system of the head and neck. The communications between the intra- and extracranial divisions are indicated.

An interesting situation reported by Duval (1909) was detailed by Evans. Following ligation of the second jugular the face became not only violet but black. The discoloration extended down to the neck and respirations ceased. Suddenly a profuse hemorrhage of black blood from the mouth and throat occurred, the patient resumed breathing, the face became violet and then pink and the patient eventually made a good recovery. Apparently the spontaneous venesection allowed for adjustment of the intracranial hemodynamics sufficient to carry the patient over this critical period.

Ligation of both internal jugular veins for lateral or sigmoid sinus thromboses was reported in three cases. All recovered without important residuals. Evans concluded that there is no good reason for avoiding bilateral jugular ligation in such instances because sufficient collateral circulation is soon established and serious sequelae are rare. Since ligation was performed at a high level in these patients, they are not comparable to those in whom bilateral complete removal of the internal and external jugular veins has been done.

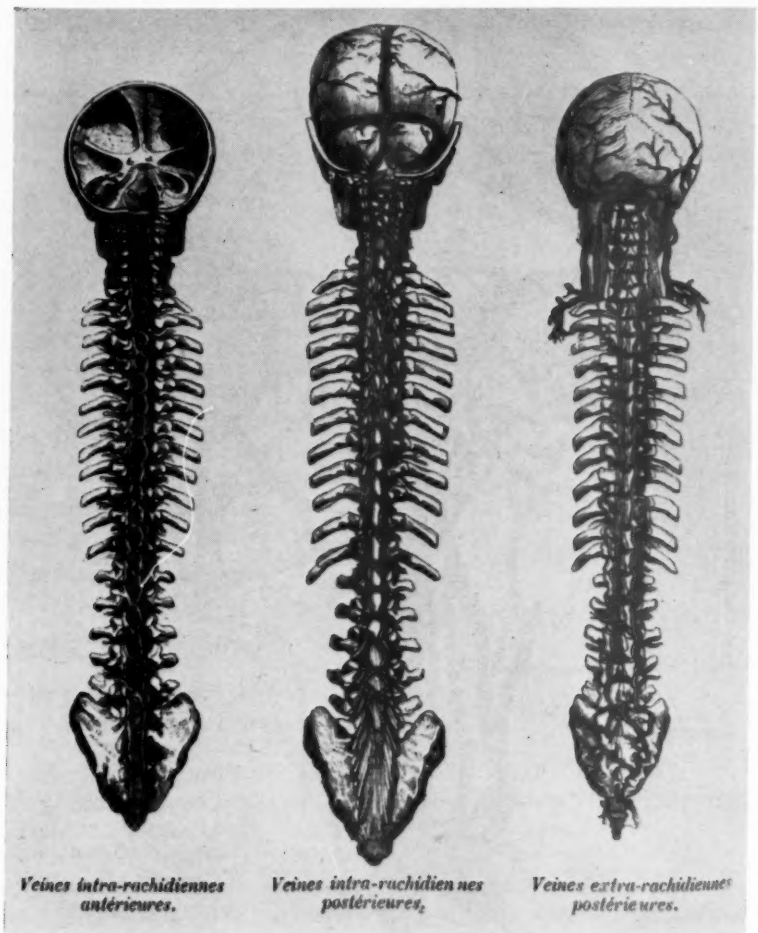

Fig. 3.—The vertebral veins extend from the cranium to the coccyx. There are many communications with other veins. (From Sappey, P. C.: Traite d'Anatomie, Paris, 1869, p. 754.)

Batson[3] stated that he had studied three cases of effort thrombosis involving the vessels at the root of the neck in which satisfactory venous compensation, apparently through the vertebral system of veins, had occurred.

The observation has been made that following strangulation from hanging, the face and neck are greatly congested with blood while the brain appears anemic.[5] This suggests that the intracranial and vertebral venous communications are sufficient to allow complete drainage of blood from the intracranial but not the extracranial structures when the body is in the vertical position.

The most acceptable therapy for cancer of the head and neck is wide surgical excision. Radical neck dissection involves removal of the superficial and deep cervical structures including the sternomastoid muscle, the external and internal jugular veins, and the entire block of tissue containing the superficial and deep cervical lymphatics. Complete dissection cannot be achieved

Fig. 4.—Radiographs of newborn cadaver after injection of a solution of sodium iodide into the longitudinal sinus. The neck has been tightly compressed by a circular bandage as indicated by the arrow. *1* and *2*, Before injection; *3* and *4*, after injection of 5 c.c.; *5* and *6*, after injection of 7.5 c.c. Note filling of systemic vessels and heart.

without removing the internal jugular from the base of the skull to the base of the neck. If such is true in unilateral neck dissection it would seem to apply in bilateral dissection. That such is accepted practice is indicated by several communications.[7, 8, 9] There appears to be no uniformity of opinion regarding the time interval between the first and second sides. Although this will be conditioned by existing local and general factors a minimum elapsed time of one to two weeks would appear desirable.

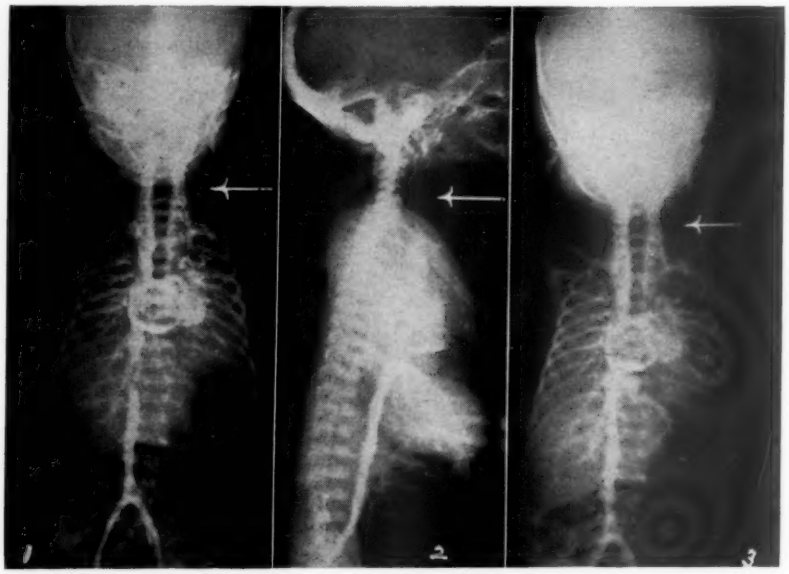

Fig. 5.—Preparation similar to Fig. 4. Note the well-filled vertebral veins when all other cervical veins have been closed by compression.

INJECTION STUDIES ON THE CADAVER

The vertebral venous connections between the head and great vessels of the trunk were demonstrated by radiographic studies. Stillborn or recently dead infants were used. The bodies were suspended vertically until the venous blood had drained from the cranium. A tight compression bandage was then applied the full length of the neck. The superior longitudinal sinus was cannulated and saturated solution of sodium iodide was slowly injected with minimum pressure in 5, 7.5, and 10 c.c. amounts. Radiographic exposures in both the anteroposterior and lateral view were made after each injection.

In all instances some immediate filling of the heart and great vessels was observed. The vertebral plexus was seen as a continuous network of small channels extending along the lateral vertebral area down to the mediastinum where the media entered the systemic veins (Figs. 4 and 5). As the amount of injection media was increased, further filling of the intracranial venous sinuses, the large systemic veins, and the jugular system both above and below the constricted area occurred. When the bandage was removed the jugular veins filled. These studies will be detailed in a subsequent report.

CASE REPORTS

CASE 1.—V. F. (R62042), a white man 54 years of age, was admitted to the Veterans Hospital in February, 1939, complaining of a lump in the right side of the neck, which had been present about one year. There was a mass about 4 cm. in diameter located beneath the insertion of the right sternomastoid muscle. A right radical neck dissection* was done on Feb. 13, 1939. Diagnosis was branchiogenic carcinoma. Postoperatively the patient received radiation therapy to the right side of the neck. The patient was carefully followed. In March, 1945, a mass in the left side of the neck of four weeks' duration was noted. A left radical neck dissection was done on March 12, 1945. The pathologic diagnosis was metastatic carcinoma from branchial cleft cyst. Following the second operation there was recurrent headache but no edema of the face or head. In July of 1947, he complained of hoarseness. A laryngeal biopsy revealed metastatic carcinoma and the patient was treated with irradiation to each side of the larynx. Biopsy of the larynx was again performed in March, 1949, and a diagnosis of lymphoepithelioma was made. Further therapy was given. Upon review of all sections, the diagnosis was made of epidermoid carcinoma of branchial cleft origin. Examination on Nov. 8, 1949, revealed no evidence of persistent disease.

On two occasions venograms were made following injection of 25 c.c. of Neo-Iopax into a frontal vein. The anteroposterior and lateral views demonstrated many small channels at the region of the pterygoid fossa and base of the skull with rapid flow into two main channels, which appear to be dilated vertebral and profunda cervical veins (Figs. 7 and 8).

The cerebrospinal fluid pressure is 140 mm. Hg and the Cone test shows a normal response. There is no evidence of papilledema. There is some cyanosis of the face and head, as well as headache when the head is placed in the dependent position. There is slight chronic puffiness of the face (Fig. 6).

CASE 2.—M. H. (R64316), a white man, 27 years of age, was admitted to the Veterans Hospital on Jan. 17, 1947, complaining of persistent hoarseness since December, 1944. Repeated biopsies of the larynx were performed before the diagnosis of carcinoma of the larynx was established. X-ray therapy was instituted but later abandoned because of edema of the cords. A tracheotomy with subsequent laryngofissure was done. Later, biopsy revealed persistent carcinoma and a total laryngectomy† was done on May 29, 1947. The postoperative course was uneventful.

In May, 1948, a slowly enlarging mass above the right clavicle was noted. A right radical neck dissection was performed. The specimen revealed metastatic epidermoid carcinoma diffusely infiltrating the lymph nodes. A portion of the skin flap sloughed and a split-thickness skin graft was applied to this area. This was followed by a total of 2,500 r applied to both right and left cervical areas.

On Feb. 22, 1949, the patient was readmitted for treatment of a 1 cm. nodule to the left of the thyroid cartilage, believed to be a metastatic tumor. A left radical neck dissection was done on March 2, 1949. The pathologic diagnosis was abscess without tumor cells.

Following the second neck dissection the patient had very severe cyanosis and edema of the face and head. Continuous headache persisted for several weeks and he was unable to rest in the horizontal position. At the present time, there is edema of the face and head which fluctuates in degree (Fig. 9). The patient observes that his face is swollen "like a balloon" if he lies flat overnight. Working or other activity results in decreased swelling. There are no veins visible on the face or scalp. There are no alterations in vision or cerebration. The patient has abnormal sweating of the face and head. Venograms and cerebrospinal fluid pressure studies have not been obtained.

CASE 3.—J. V. (R64843), a 39-year-old white man, was admitted to the Veterans Hospital in April, 1947, complaining of a lesion of the tongue of seven months' duration. There was an elevated area of leucoplakia 3.5 cm. diameter extending from the midportion of the

*Operations were performed by Dr. George Pfeiffer.
†Operations were performed by Dr. R. A. Wise.

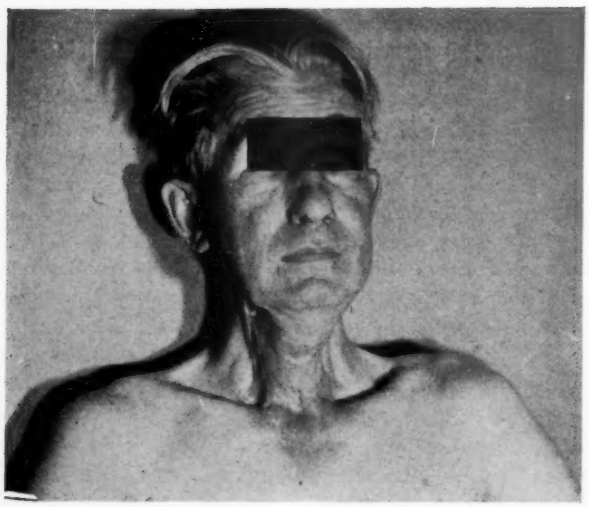

Fig. 6.—Case 1. Four years after operation on second side. Note minimal puffiness of face.

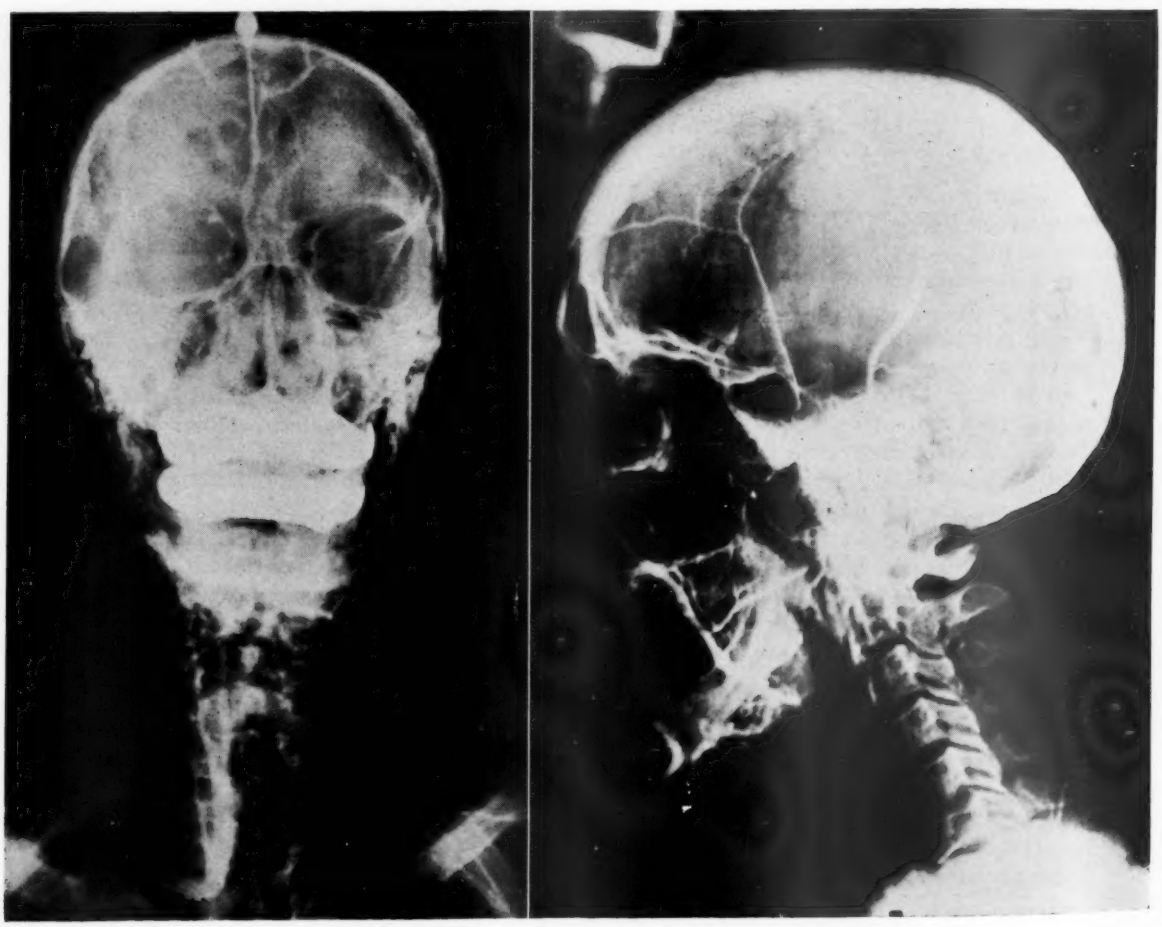

Fig. 7. Fig. 8.

Figs. 7 and 8.—Venograms in Case 1. Note large channels in the neck in the anteroposterior view. Multiple small channels are apparent in the lateral view.

tongue to the left anterior pillar. There was no ulceration. A few small nodes were palpable in the left submaxillary area.

Biopsy of the tongue showed keratinizing squamous-cell carcinoma. Radon seeds were implanted and a left radical neck dissection* was done on August 25, 1947. No tumor cells were found in the operative specimen. He was seen at frequent intervals in the tumor clinic and was readmitted in April, 1948, for a rapidly growing tumor of three weeks' duration overlying the right sternomastoid muscle. Right radical neck dissection was performed on April 28, 1948. Pathologic examination revealed metastatic anaplastic squamous-cell carcinoma with invasion of the internal jugular vein. Postoperatively, the patient's face was markedly cyanotic for six hours. Edema of the face was also marked and persisted for two weeks.

In August, 1948, the patient was given x-ray therapy to the right cervical area. On March 31, 1949, a small nodule near the angle of the right jaw was excised and found to be foreign body granuloma. Biopsy of the tongue on Dec. 20, 1949, revealed persistent epidermoid carcinoma. A partial glossectomy was done.

The patient has had no chronic headache, no visual disturbances, and no edema. There is cyanosis when the head is placed in the dependent position. An anteroposterior venogram revealed a rapid flow of the contrast media from the extracranial veins into the small veins of the neck. Their precise location cannot be determined from the radiographs.

Fig. 9.—Case 2. Note puffiness of the face. This is somewhat accentuated by a thin neck.

CASE 4.—J. L. (R64785), a 20-year-old white man, first noted a mass in the neck in 1946, while overseas. Biopsy was said to have revealed a malignant adenoma of the thyroid. Elsewhere in July, 1947, biopsy of the thyroid and a left supraclavicular lymph node was performed. Pathologic diagnosis was grade 1 carcinoma of the thyroid with metastasis. The patient then received irradiation to the neck and later was given 3,000 microcuries of radioactive iodine. On October 20, 1947, a left radical neck dissection was done but the thyroid was not disturbed. Carcinoma was found in the lymph nodes at this time. Following this the patient was given 6,797 microcuries of radioactive iodine which produced hypothyroidism without regression of the tumor.

He was admitted to the Portland Veterans Hospital on March 28, 1949. There was a low transverse neck scar and a scar from a left mastoid process of the sternal notch. Extensive induration was noted throughout the lower cervical region and a mass was felt along the right sternomastoid muscle, as well as a questionable mass at the bifurcation of the right common carotid artery. Laryngoscopic examination revealed bilateral recurrent nerve paralysis.

On April 1, 1949, tracheotomy,† right radical neck dissection, and excision of the right lobe of the thyroid were performed. Pathologic diagnosis was carcinoma of the thyroid with

*Operations were performed by Dr. R. A. Wise.
†Operation was performed by Dr. R. A. Wise.

metastasis to the lymph nodes. Postoperatively the patient's course was uncomplicated. There was no cyanosis and but slight edema of the face. There was no headache, visual disturbance, or other evidence of vascular embarrassment. Placing the head in a dependent position caused no visible discoloration of the face. At the present time the patient has some puffiness of the face. There is no evidence of persistent tumor and the tracheotomy has closed.

Fig. 10.—Venogram in Case 5. Note multiple suboccipital veins and the lateral cervical channel.

CASE 5.*—E. W., a 51-year-old man, was seen by his local physician in September, 1947, for a nodule in the right side of the lower lip. He received irradiation therapy. There was no biopsy. In March, 1948, swelling in the right submaxillary area followed by a similar swelling on the left was observed. In October, 1948, the patient presented himself with a 4 cm. cystic mass in the suprahyoid area. The mass was excised, with drainage of a large quantity of blood and necrotic material. Biopsy from the wall of the mass revealed metastatic squamous-cell carcinoma. On Dec. 9, 1948, a bilteral suprahyoid dissection was performed and was followed on Dec. 29, 1948 by tracheotomy and left radical neck dissection. On Jan. 13, 1949, a right radical neck dissection was performed. The deep cervical nodes on both sides were found to be involved by the carcinomatous process. Healing on the right was slow, and eventual extension to the mandible and the soft tissues of the neck occurred. Prior to death in March, 1949, there was marked edema and cyanosis of the face as well as severe headache. There was no autopsy.

A venogram taken in the lateral position before edema became prominent revealed numerous suboccipital channels communicating with the vertebral veins, a long cervical lateral vein, and many small tributaries probably representing communications of the pharyngeal, esophageal, and subcutaneous plexuses (Fig. 10).

*Case from the files of Dr. R. M. Coffey.

CASE 6.—J. S., a man 65 years of age, was admitted to Multnomah County Hospital on May 28, 1948, for proved squamous-cell carcinoma of the right side of the lower lip. A V excision followed by a suprahyoid dissection was performed. The submental nodes contained tumor cells. A right radical neck dissection* was performed Dec. 20, 1948. Metastatic tumor cells were found in one of eight nodes. During subsequent follow-up examination enlarging nodes were noted on the left. On Feb. 10, 1949, a left radical neck dissection was performed for presumed metastases. Marked hyperemia without metastases to any of the twenty-six nodes examined was reported.

Postoperatively there was some edema, increased discoloration of the face, as well as severe headache for several days. Prior to operation on the second side the spinal fluid pressure was 150 mm. and the Cone test was normal. At operation large dilated veins were encountered anterior to the deep neck muscles. Four hours following operation the cerebrospinal fluid pressure was 130 mm. with normal rise on cough. Four days later the pressure was 40 mm. with 10 mm. rise on straining. The fundi showed no papilledema. There is puffiness of the face but no cyanosis or headache and the patient has remained well (Fig. 11). The venogram in the anteroposterior view revealed a single, well-filled, tortuous vein extending the full length of the neck, where it communicated with a transverse cervical vein. A second larger but less well-filled channel paralleled the first in part of its course. It is probable that these represent a vertebral and deep cervical vein respectively (Fig. 12).

Fig. 11.—Case 6. Note moderate edema of face.

CASE 7.—J. K., a man 50 years of age, was first treated for conjunctival melanoma of the left eye in 1944. Multiple operations were performed and complete removal of the orbital contents was accomplished in 1948. The patient was admitted to Multnomah County Hospital in January, 1949, for a mass in the left anterior auricular area. A left preauricular block dissection† including the parotid gland was performed. Metastatic melanoma was found in the lymph nodes. On Feb. 17, 1949, a left radical cervical dissection was carried out again with the removal of involved nodes. Subsequently, enlargement of the lymph nodes in the right cervical chain was noted and on April 28, 1949, a right radical dissection was done. The specimen showed only chronic lymphadenitis without metastatic involvement.

Following operation there was some edema of the face and head as well as cyanosis of these structures. There was no obvious visual impairment. Just prior to operation on the second side the cerebrospinal fluid pressure was 220 mm. of water and the response to the Cone test was normal. Six hours after operation, the cerebrospinal fluid pressure was 390 mm. of water. Three weeks following completion of the second operation the patient de-

*Operations were performed by Dr. C. G. Peterson.
†Operations were performed by Dr. C. G. Peterson.

veloped signs of cord compression with complete block at sixth to seventh dorsal vertebrae. Radiographs revealed compression of the seventh dorsal vertebrae. A laminectomy was done with the discovery of extradural vertebral metastasis completely surrounding the cord. There was reason to believe that bilateral jugular excision had in some manner contributed to this bizarre type of metastatic spread, probably through the vertebral veins. The patient expired on June 7, 1949. Autopsy revealed no cerebral edema, cerebral venous congestion, or evidence of increased cerebrospinal fluid pressure. Metastatic involvement of the liver, lungs, and upper dorsal vertebrae was demonstrated.

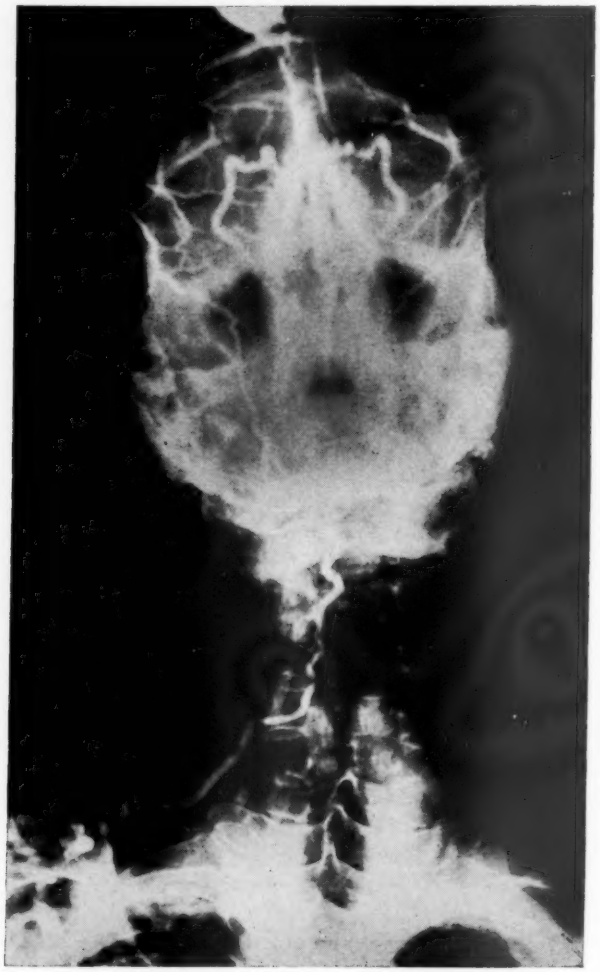

Fig. 12.—Venogram in Case 6. Note the well-filled large tortuous vein traversing the entire neck. There is also a second collateral which is less well filled.

CASE 8.*—This man, 55 years of age, had had a total laryngectomy for cancer of the larynx in 1946 and had received irradiation therapy to the neck. In 1947 enlarged lymph nodes were noted in both the right and left neck. A left radical neck dissection was followed in seven weeks by a right radical neck dissection. An attempt was made to spare the right internal jugular vein but carcinomatous infiltration made its removal necessary. During the operative procedure the patient's face was covered. When the drapes were removed it was found that the face was extremely cyanotic and edematous. There were many bullae

*Case from the files of Dr. Allan Boyden.

of the conjunctiva. Severe edema and discoloration of the face persisted for two days then receded somewhat. During this time the patient had unbearable headache and was unable to sleep even in the sitting position. Edema and discoloration of the face with headache persisted following discharge from the hospital. The patient was unable to remain in the horizontal position. It was observed that excitement, exertion, or laughing would cause extreme suffusion of the face. Three months following the second procedure a skin nodule was excised and the area was grafted. Incomplete healing was followed by a fatal hemorrhage after he had returned to his home. No post-mortem examination was done.

DISCUSSION

It is noteworthy that no malignant cells were found in the tissues removed at operation from one side in four instances. In Case 3 no metastases were found in the lymph nodes at operation on the first side. In Cases 2, 6, and 7, no metastases were found in the specimen removed from the second side although the first side was positive. This would indicate the need for biopsy and histologic verification where the diagnosis is uncertain. It is conceivable that following unilateral dissection lymphatic hyperplasia on the opposite side may simulate metastatic involvement.

That spread of metastases via the vertebral system of veins may occur following interruption of the jugular veins is suggested by observations in Case 7. Osseous metastases are unusual in melanomas; however, three weeks postoperatively rapidly advancing cord compression due to a metastatic lesion of the dorsal vertebrae was noted. At autopsy there was widespread involvement of the viscera and dorsal spine. Although we are unable to establish the absence of vertebral metastases prior to the second neck dissection the postoperative course strongly indicates this to be a factor precipitating spread to these structures.

In all cases (Table I) varying degrees of edema of the face was observed. Edema of the face gradually receded during the immediate postoperative period but some permanent puffiness of the face persisted in most cases. This has been of sufficient degree in Case 2 to be termed by the patient himself, "fat face."

Facial discoloration from a pink to a cyanotic hue was common immediately following operation but regressed more rapidly than did edema. Severe headache often persisted for several days. Later, headache would recur if the head were placed in the dependent position. Most individuals preferred to sleep with the head elevated.

Visual disturbances did not occur in this series. The eye grounds were found to be normal in two patients after other signs indicated vascular adjustments had occurred.

The cerebrospinal fluid pressure was elevated from 220 mm. of water preoperatively to 390 mm. of water six hours after operation in Case 7. In Case 6 the cerebrospinal fluid pressure was 150 mm. prior to operation and 130 mm. four hours following operation. In Case 1 cerebrospinal fluid pressure was normal four years after operation. No conclusions can be drawn from these observations but no clinical evidence of severe or permanent elevation of cerebrospinal fluid pressure was noted in this series.

TABLE I. SUMMARY OF CASES

CASE NUMBER	PRIMARY LESION	INTERVAL BETWEEN TWO SIDES	METASTASES IN SPECIMEN	IMMEDIATE EFFECTS	LATE EFFECTS	COMPENSATION
1.	Branchiogenic Ca.	6 years	Side 1, Pos. Side 2, Pos.	Edema of face, headache	Slight, edema, headache on dependency	Good, 4 years
2.	Ca. larynx	9 months	Side 1, Pos. Side 2, Neg.	Severe edema of face, cyanosis, headache	"Fat face," rubor	Fair, 11 months
3.	Ca. tongue	8 months	Side 1, Neg. Side 2, Pos.	Marked edema of face, cyanosis 6 hours	No permanent changes	Good, 21 months
4.	Ca. thyroid	18 months	Side 1, Pos. Side 2, Pos.	Slight edema of face	Puffiness of face	Good, 9 months
5.	Ca. lip	1 month	Side 1, Pos. Side 2, Pos.	Moderate edema	Disease progressed with increasing edema	Died of disease, 2 months
6.	Ca. lip	2 months	Side 1, Pos. Side 2, Neg.	Moderate edema, rubor	Slight puffiness of face	Good, 11 months
7.	Melanoma of conjunctiva	2 months	Side 1, Pos. Side 2, Neg.	Edema of face, cyanosis	Disease progressed, vertebral metastases	Died of disease, 2 months
8.	Ca. larynx	7 weeks	Side 1, Pos. Side 2, Pos.	Extreme edema with bullae formation, extreme cyanosis, severe headache	Moderate edema, severe cyanosis on dependency	Died of hemorrhage, 4 months

Venous pressure in the superficial veins was not determined. That the superficial veins of the head and face are not abnormally prominent may be attributed early to obliteration from edema of the superficial structures and later to functional adequacy of the collateral veins.

Demonstration of some of the deep channels of the neck was accomplished by venographic studies. The limitations of injection studies of the head in living persons are obvious. The procedure may be hazardous and is attended by unpleasant reactions which makes repeated studies difficult to obtain. The finer channels such as those of the vertebral plexus are not usually sufficiently filled for radiographic visualization. Likewise, the intracranial, extracranial, and deep cervical communications cannot be satisfactorily filled by injecting the superficial veins of the scalp. Introduction of the media into the intracranial venous sinuses, though desirable, is impractical.

Radiographic studies on infant cadavers to some extent have supplemented our knowledge of the vertebral plexus. Preliminary studies show this network to be capable of conveying large amounts of blood.

Although the adequacy of the communicating channels of the head and neck were not determined preoperatively in the present series this would seem to be a logical procedure. The remaining jugular could be compressed without disturbing the deep cervical veins. At this time subjective and objective observations could be made. Venous and cerebrospinal fluid pressure studies should be done in different positions. If evidence of severe venous insufficiency were found consideration should be given to sparing the second jugular. Even

though intermittent or continuous compression of the jugular may favorably influence flow through the collateral channels and aid the venous adaptation preoperatively, the hazard of lymphatic or venous extension of the disease would seem to preclude use of this procedure.

SUMMARY AND CONCLUSIONS

1. The venous system has a remarkable ability to adapt to bilateral removal of the jugular system. In the head the adjustment involves the intracranial, communicating, and extracranial venous elements. In the neck the vertebral plexus of veins appears to be the principal by-pass after removal of the jugular system.

2. Removal of the second jugular system is followed by partial decompensation of the venous circulation. This is manifested by edema and discoloration of the face, headache, and inability to maintain the horizontal position. As venous adaptation occurs various degrees of compensation return. A permanent "fat face" may be expected in some cases.

3. The effect of bilateral jugular removal on cerebrospinal fluid pressure cannot be stated on the basis of these observations but in this series no serious alterations were noted.

4. It is suggested that unilateral neck dissection may result in contralateral lymphatic hyperplasia simulating metastatic spread.

5. There is reason to believe that in the presence of uncontrolled disease bilateral jugular removal may facilitate spread of metastases through the vertebral venous plexus to bone.

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DISCUSSION

DR. B. RAY.—I should like to report on some work we have been doing recently that is, I think, related to this admirable work that Dr. Gius has just reported.

We have done ours for a different purpose, but the two link together. We have been catheterizing the sagittal sinus through a burr hole just in front of the hairline, and through that catheter injecting a contrast dye, Diodrast, and taking x-ray pictures showing the filling of the venous system. This has been a particularly interesting study thus far, and we find that no two people look alike exactly in their venous arrangement.

Our interest, of course, had to do with finding out before an intracranial operation whether the sagittal sinus or other sinuses were occluded by, say, a meningioma. We also

have been interested in determining the existence of thromboses in patients who have so-called pseudotumor with increased intracranial pressure.

We find that in normal individuals there is considerable variation—this is not new—but we find that often the dye introduced here will go down only one jugular system and does not get into the other one at all, indicating that in many people there must be a dominance of the venous drainage on one side. That being the case, if one were concerned about avoiding the symptoms and signs that Dr. Gius has related to you, he might consider leaving the jugular on that side or, if he were bolder, he might even put in a vein graft.

I think studies of this kind are very much needed. There has been a lot of loose thinking about what one can do in interrupting the venous drainage from the head with safety and Dr. Gius' work is certainly in the right direction.

DR. J. MODLIN.—At the Ellis Fischel Cancer Hospital, twelve bilateral total neck dissections have been performed during the past ten years. In six of these patients, the internal jugular vein was removed bilaterally. These were staged procedures with an average interval between operations of at least four weeks. Although there was no immediate operative mortality in this group of six patients, as was indicated by Dr. Gius, there was a rather alarming immediate postoperative edema of the face, conjunctiva, and laryngopharynx necessitating the maintenance of a tracheostomy opening for periods up to three weeks. Because of this, the internal jugular vein has been preserved on one side in the last six bilateral total neck dissections, the sheath of the vein being removed much as in a radical mastectomy. In the latter group of cases, the alarming sequelae which follow bilateral jugular resection have been absent. In most cases, an adequate lymph node dissection can be accomplished with preservation of the vein and it would thus appear that whenever possible the vein should be preserved on one side.

DR. H. ROYSTER.—We have had five patients who have had the same operation, the earliest one about four years ago. Two of the patients have succumbed due to the primary disease, which was cancer of the mouth. I can say the same symptoms occurred. The first signs of swelling were very alarming.

Since we have been doing more tracheotomies for the usual radical sections, and I see Dr. Gius does the same, we compress the neck very tightly with a bandage, and even after the first radical neck dissection, there is a great swelling of all the tissues above the dressing, and alarmingly so at first.

We have not had any patient who showed immediate effects of the tight compression, but we have had two patients, who died within three weeks, who had had unilateral resections with moderately tight bandages around the head and neck. At post-mortem, no reason for the death could be found: neither pneumonia—which is not uncommon—nor any lesion in the brain.

I was wondering whether there might not have been temporary blockage or something, as Dr. Ray has described, which produced a physiologic change in the brain which did not show up at post-mortem. So it may be possible with a tight dressing and a unilateral resection to get into some difficulty of that sort.

DR. O. V. BATSON.—In a series of phlebograms obtained following the injection of a roentgenopaque medium into forearm veins, I found that often the injected material fails to reach the superior vena cava from the subclavian vein. Instead it leaves the subclavian vein through several channels to reach the lower cervical vertebral plexus of veins and progresses to the thoracic cavity through the vertebral plexus. I assume that the patients held their breath as instructed, perhaps even strained a little. This increased the intrathoracic pressure and prevented the flow into the superior vena cava.

These phlebograms showed that the vertebral venous plexus was much more than an emergency network. It is used as a pathway from the head and neck and the upper extremities every time we forcibly hold our breath. Those doing lifting and straining, miners and freight handlers, for example, should have better developed vertebral vein anastomoses than sedentary workers, and should be disturbed less by the acute ligation of the jugular

veins. Recall that except for a few minor vessels around the larynx, the veins of the head and neck are without valves, hence there can be no constant direction of flow in any head and neck vein.

In the last fifteen years the heroic measures formerly carried out for complications of mastoid disease have been forgotten. Bilateral jugular vein ligation was performed in patients with dural venous sinus thrombosis with good results.

Even acute occlusion of the superior vena cava, equivalent to ligation, need not be fatal. I have had the opportunity to examine and study four of these cases. All presented definite changes as a result of the occlusion but these changes decreased with time, due to the enlargement of anastomotic channels. Even without enlargement enough anastomoses are present in some to substitute immediately for both subclavian veins and the vena azygos major in addition to both internal jugular veins.

The edema reported must be similar to that which follows when both the venous and the lymphatic drainage is blocked. Razor cuts and burrowing ulcers of the neck may give edema of the face. In breast resections the removal of axillary lymphatics with the ligation of the axillary vein is generally followed by lymphedema of the upper extremity distal to the field of operation.

The anatomy of the venous system is favorable for bilateral jugular vein ligation and after the paper of Dr. Gius and the discussion evoked, it would seem there need be no great fear of ligation of both internal jugular veins when conditions demand.

AN IMPROVED METHOD OF VENOGRAPHY FOR THE PREOPERATIVE EVALUATION OF THE POSTPHLEBITIC EXTREMITY

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THE chronic pathologic changes of the postphlebitic extremity—edema, dermatitis, pain, varicosities, and ulceration—have long proved to be of physical and financial concern to the patient and an almost insurmountable problem of treatment to the physician and surgeon. The multiplicity of forms of local conservative therapy and simple or extensive surgical procedures have proved that no one form of therapy may be expected to be successful in all cases.

There is little doubt that all the postthrombotic changes are a result of sustained increased venous pressure due to complete deep obstruction or retrograde pressure following recanalization.[1, 2] The latest and most promising surgical procedure, interruption of the recanalized femoral vein, has been proved by Homans,[3] Linton,[1] and others[4, 5, 6] to be a physiologic therapeutic approach to the latter problem. Acting on the same premise, Bauer[2] has excised the popliteal vein in similar cases. All patients presenting these physical findings, however, do not exhibit the same underlying pathology.

Unlike other procedures, which reflect indirectly the status of deep veins, venograms provide visual evidence of normal and abnormal vessels. The demonstration of the course and characteristics of vessels by intravascular injection of radiopaque materials has been reported with many variations since Berberich's and Hirsch's original report in 1923.[7] More recently retrograde methods of femoral vein injection have been described to demonstrate the outline and dynamics of deep veins.[2, 4, 6, 8] Selection of single or combined therapeutic procedures should be based on a thorough preoperative study of each individual problem. Prompted by the need for adequate preoperative diagnostic measures in the proper choice of methods of treatment of the postphlebitic extremity, we have developed an improved method of venography. The technique is believed to represent an aggregation of many refinements which provides a maximum of information with a minimum of procedure.

Seventy-five clinical problems, involving all types of chronic venous pathology of the lower extremity, have been investigated in this manner. Correlation of x-ray findings with history and physical examination has made possible individualization in the selection of proper types of treatment for these patients. Clear-cut preoperative indication for femoral vein inter-

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ruption was provided in thirteen cases in which recanalization was demonstrated. Gross pathology as revealed at the operating table correlated absolutely with preoperative prediction. Other problems investigated in the group included those with proved deep venous obstruction, simple varicose veins with complications, and minimal physical findings suggestive of deep venous disease. Follow-up observations have indicated the efficacy of these studies in diagnosis.

Venograms have value in the solution of three of the most common problems involving the lower extremity. Patients with a history suggestive of, and physical findings compatible with, a former episode of deep vein thrombosis may be evaluated.

1. In those found to have a normal deep venous circulation, attention may be directed to treatment of local pathology and superficial varicose vein disorders.

2. Problems of complete deep venous obstruction may be separated from those of partial obstruction or recanalization. Unnecessary deep vein exploration in the former is avoided and therapy may be directed to that portion of the collateral system responsible for symptoms.

3. Determination of which deep veins below the knee connect directly with the tributaries of the recanalized femoral vein may be made. This indicates the ligation of those veins necessary to relieve the orthostatic effect on the involved extremity.

METHOD

The patient is tested for sensitivity to Diodrast. The intradermal injection has been proved effective for preliminary elimination of sensitive reactors to the drug. All patients with a negative reaction to the skin test are given a "scout" intravenous injection of 1 c.c. of solution. A three-minute period of observation should precede further injection.[9] We have observed only one patient in whom sensitivity contraindicated the procedure.

With the patient in the supine position, a No. 19 or 20 gauge needle is inserted into a dorsal foot vein or the greater saphenous vein below the internal malleolus (Fig. 1). Smaller needles have been used successfully in small veins. Though cannulation is rarely necessary, it is a worth-while procedure when veins cannot be entered through the skin. To the needle is attached a twelve-inch piece of small-caliber rubber tubing which has on its other end a three-way stopcock. The needle is firmly fixed in position with adhesive. Using this arrangement, syringe pressure and manipulation at the stopcock are not apt to dislodge the needle. To the free arm of the stopcock is attached an intravenous infusion set containing physiologic saline solution. This fluid serves to keep the needle and venous channel patent, and to flush the veins free of dye following injection.

Two x-ray units are employed simultaneously, a permanent tube over the upper thigh and inguinal region and a portable over the leg, with a lead shield hanging between the two fields to avoid stray radiation. The x-ray table is fixed in a horizontal position.

A rubber tube tourniquet is placed around the leg just above the malleoli, obstructing only the superficial veins, and 35 per cent Diodrast solution is injected rapidly. With the leg and foot everted, a lateral film of the leg alone is made after injection of 15 c.c. of dye. The leg is returned to its anteroposterior position, the film beneath the leg is quickly changed, the remaining 15 c.c. of dye are injected, and simultaneous anteroposterior exposures of the leg and thigh are made.

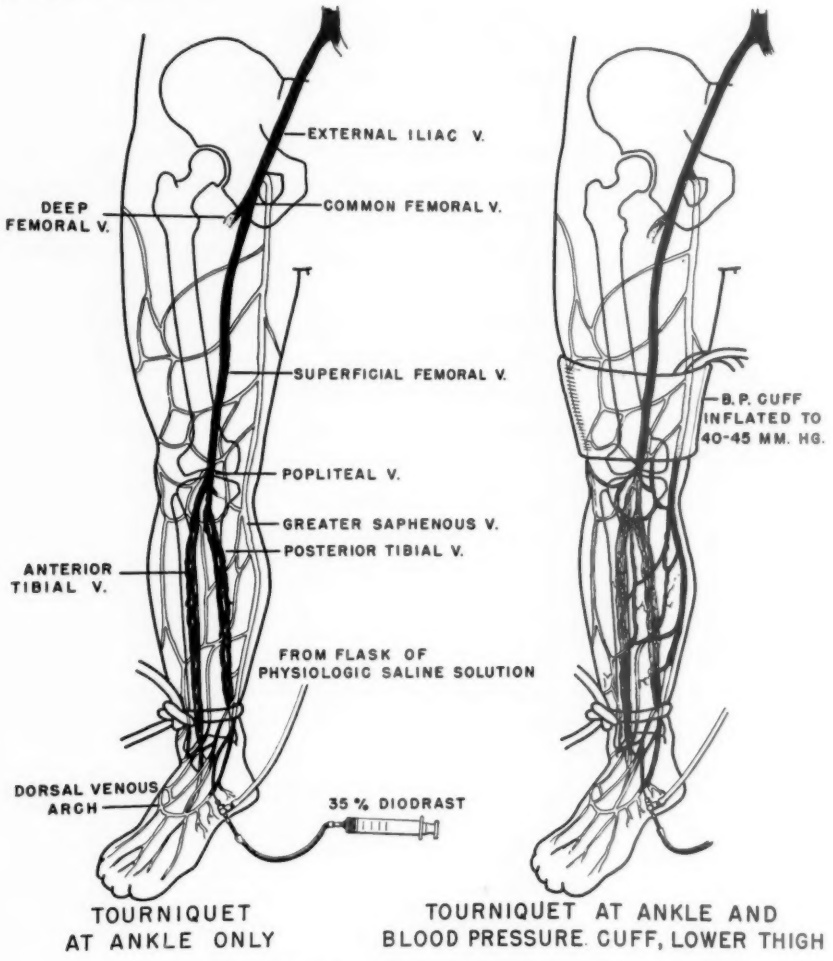

Fig. 1.—Diagram of injection technique.

If evaluation of these films reveals adequate filling and outline of a normal deep venous circulation, it is unnecessary to make any further exposures. However, additional evaluation may be necessary in those cases in which the original set of films reveals obstruction or incomplete filling of the deep veins. This may be due to passage of an appreciable portion of dye through the superficial system and/or other collateral channels.

In this event, a second anteroposterior set of films of leg and thigh are made. In addition to the ankle tourniquet as before, a blood pressure cuff is wrapped about the lower thigh and inflated to a pressure of 40 to 45 mm. of

mercury, and 30 c.c. of dye are injected. We have found this the minimal pressure necessary to obliterate always the superficial veins at this level, thereby forcing all possible dye through the deep circulation. Dye which may have entered the superficial collateral channels below the level of the cuff is thereby diverted again into the deep veins.

INTERPRETATION OF FINDINGS AND CASE REPORTS

After dye is injected into a superficial vein, it is forced into the deep veins by the ankle tourniquet, and, in the absence of obstruction, follows the shortest route to the heart. The anterior and posterior tibial veins may be seen to unite medial to the head of the fibula, and the popliteal, superficial femoral, common femoral, and external iliac veins are outlined. The embryologic development of veins of the lower extremity is responsible for frequent deviations from this normal pattern, with duplication of any of the veins, or utilization of the profunda femoris as part of the normal return channel from below the knee. Multiple bulbous distentions may indicate the location of functional valves in smaller vessels, while those in larger veins are visualized as inverted V-shaped clefts.

The superficial veins fill above the tourniquet level only when valves in the communicating veins are incompetent. Such incompetency may be due to simple varicose dilatation of the communicating veins, or the result of present or previous obstruction of the deep system with significant pressure aberrations.

Interpretation of venographic findings may be classified in the following three general categories, and case examples of each are presented.

Normal Deep Venous Circulation.—In the absence of pathology, normal veins may be expected to be smooth and regular in outline. While this is usually accomplished by the original injection procedure, the use of the blood pressure cuff about the thigh may be necessary to increase dye concentration to eliminate suggestions of pathology due to incomplete filling.

CASE 1.—W. W. (No. 21821), a 53-year-old white painter, was admitted with a ten-year history of mild varicose veins. Three years before admission he had experienced a bout of swelling, pain, discoloration, and joint stiffness of the right lower extremity, lasting several weeks. This episode was followed by chronic edema, pigmentation, and recurrent ulceration of the extremity. The only previous specific therapy had consisted of ulcer excision and grafting at another hospital, following which ulceration promptly recurred. Physical examination revealed bilateral varicosities and a large ulcer over the medial malleolus associated with brawny induration and pigmentation of the right lower leg and foot. Clinical tests revealed incompetency of superficial veins and communicating veins. The vague history suggested, but was inconclusive for, thrombosis. Venograms revealed a normal demonstration of all deep veins of the lower extremity without evidence of filling of superficial or deep collaterals (Fig. 2).

This is an example of a diagnostic problem in which the patient presented suggestive history and signs leading to suspicion of thrombosis. Normal venograms failed to support the suspicion. Assuming that the recurrent ulceration was explainable on the basis of varicosities, the ulcer was excised and segments of the greater saphenous and communicating veins were removed.

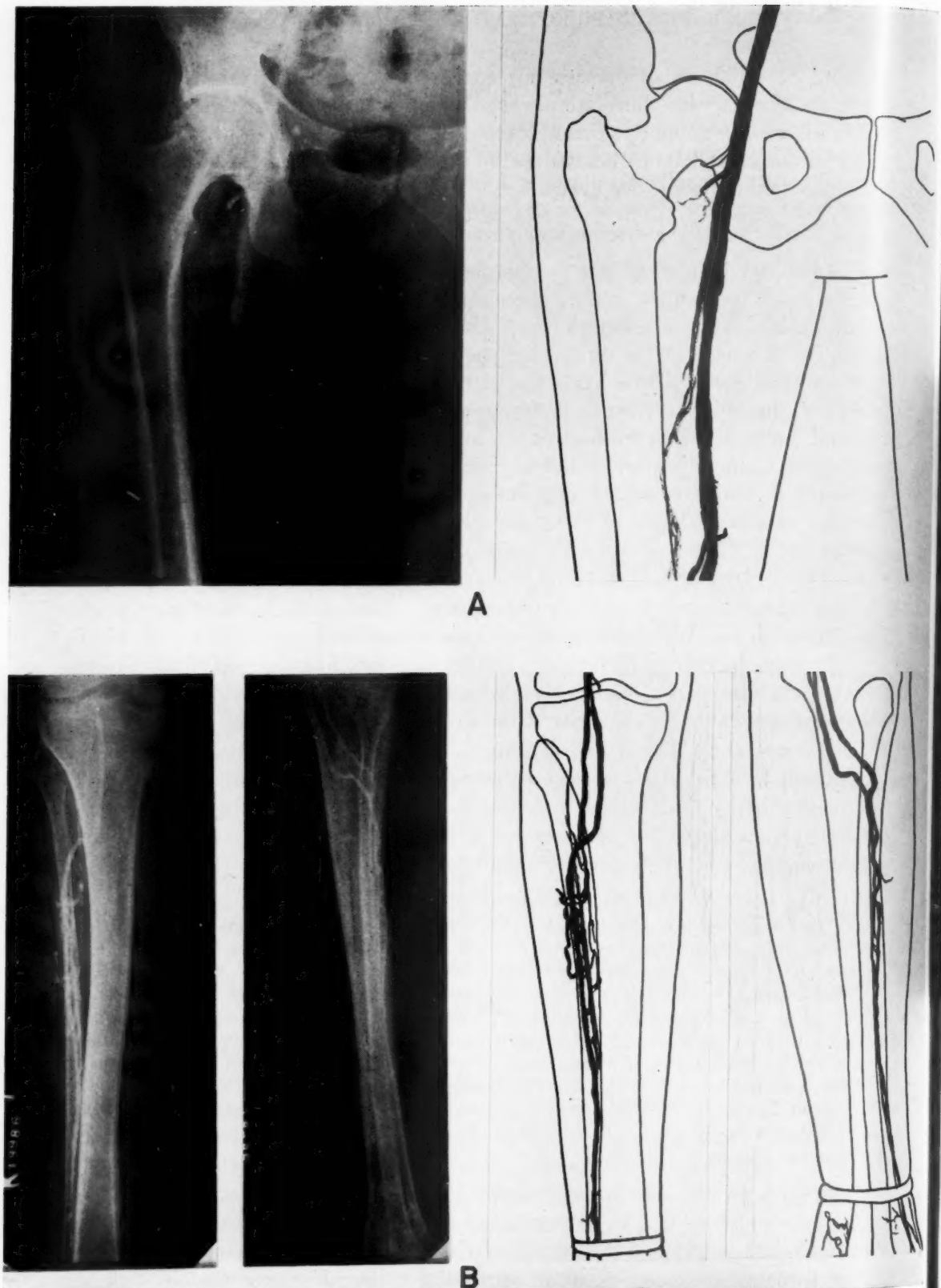

Fig. 2 (Case 1).—*A*, Venogram of thigh, tourniquet at ankle only. Normal filling of deep veins. *B*, Venograms of leg (anteroposterior and lateral), tourniquet at ankle only. Normal filling of deep veins. No superficial reflux.

CASE 2.—C. P. (No. 15774), a 35-year-old white farmer, developed mild varicosities of both lower extremities while in the Army in 1943. A year later, bilateral high saphenous ligation and retrograde injection were performed. Complaining of residual weakness and calf pain, he was admitted to this hospital six years later, presenting prominent varicosities below the knees with demonstrable incompetent communicating veins and moderate swelling. The possibility existed that symptoms might have been the result of extension of thrombosis from the superficial to the deep system, at the time of the therapeutic injection. Venograms of the leg, made with the tourniquet about the ankle, revealed adequate filling of the deep venous system without significant reflux of the dye into the superficial circulation (Fig. 3). This finding demonstrated that failure to observe such a reflux cannot rule out the existence of incompetent valves in the communicating veins, for they were proved to be present clinically, and later at operation.

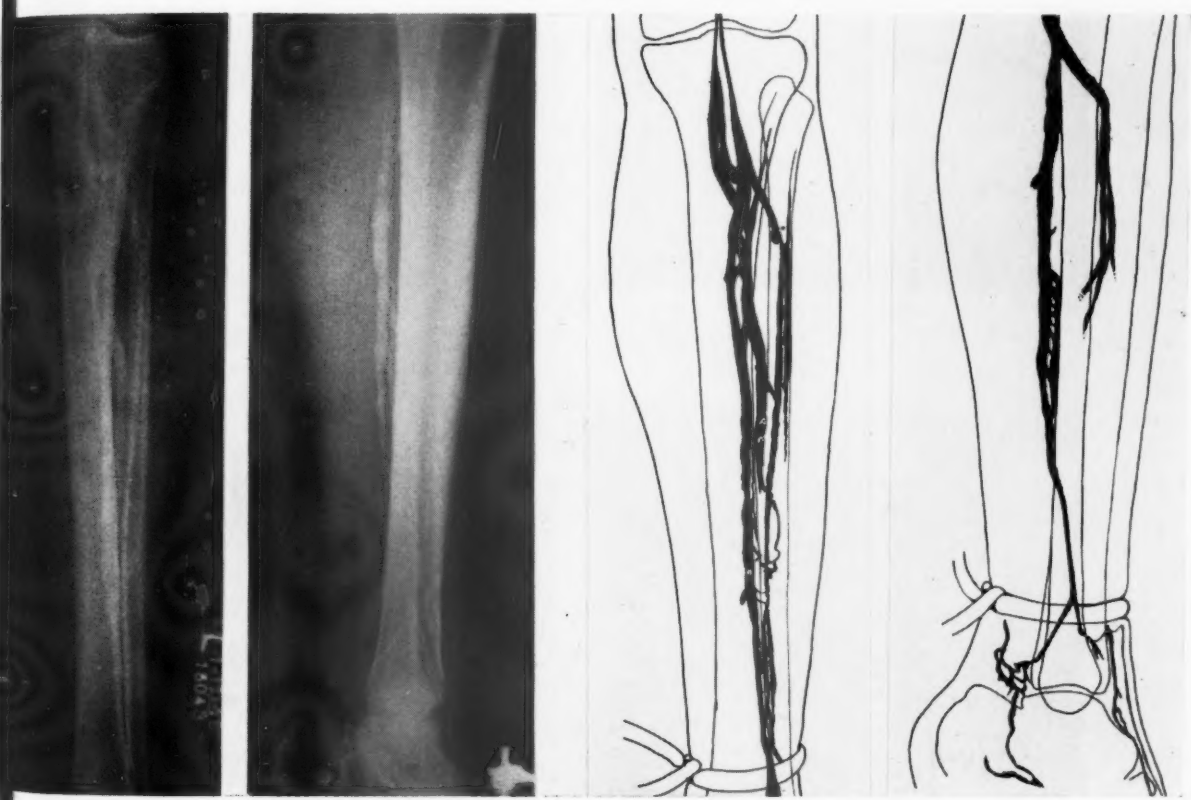

Fig. 3. (Case 2).—Venograms of leg (anteroposterior and lateral), tourniquet at ankle only. Normal filling of deep veins. No superficial reflux.

While the original film of the thigh did show the femoral vein filled with dye, its outline was irregular and the density was poor (Fig. 4, *A*). When the procedure was repeated, using a blood pressure cuff about the lower thigh, a good concentration of dye was seen through the femoral veins, outlining it sharply and revealing the presence of several normal-appearing valves (Fig. 4, *B*).

Finding that the deep veins were not impaired, it was felt that his varicosities were due only to incompetent saphenous vein valves and did not represent collateral circulation around a point of deep obstruction. The greater saphenous vein was excised and communicating veins were individually ligated. The patient is asymptomatic fourteen months after operation.

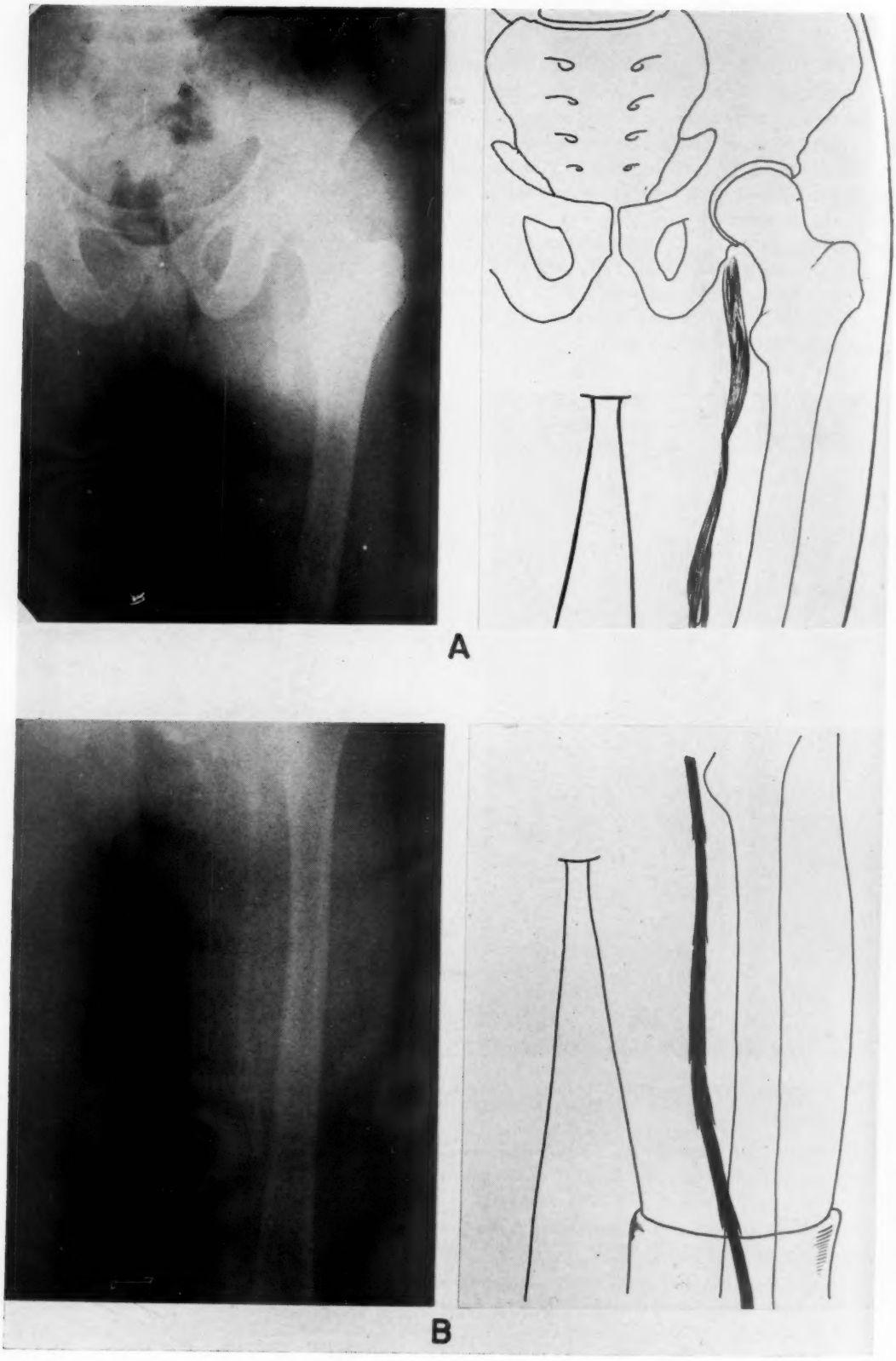

Fig. 4 (Case 2).—*A*, Venogram of thigh, tourniquet at ankle only. Incomplete deep filling. *B*, Repeat film with tourniquet at ankle and cuff about lower thigh. Complete filling of normal deep veins.

In this case, use of the blood pressure cuff proved the existence of a normal deep venous circulation after the original films suggested impairment of these veins. Venograms indicated the safety of, and necessity for, excision of superficial veins.

Deep Venous Obstruction.—In the event of a former thrombosis with residual complete deep venous obstruction, dye may be seen to proceed to this point, and only by way of collaterals to by-pass the obstruction. In such instances, it is extremely important for the surgeon to know the exact level of the obstruction and the role that individual collateral veins are playing to compensate for it. Many of the superficial varicose veins arise at the time of acute need during the old thrombosis. They now remain as derelicts of the emergency situation, not only useless but harmful. Venograms prove effective to indicate the level below which superficial veins may be safely excised in procedures to eliminate ulceration.

Case 3.—I. McB. (No. 17401), a 29-year-old man, sustained a fracture of the right humerus while in combat in 1945, and during hospitalization developed acute thrombophlebitis of the right lower extremity. Persistent swelling, chronic ulceration, and intermittent cramping pain led to his admission to this hospital three years later. There was no clinical evidence of varicose veins. The area of ulceration healed promptly under conservative treatment. Venograms revealed complete obstruction of the deep venous circulation in the right thigh, with collateral circulation by way of the superficial system to the common femoral and external iliac veins, and by way of the lateral femoral circumflex vein to anastomosing vessels about the hip (Fig. 5, *A*).

To confirm the absence of recanalization of the thrombosed femoral vein, the series was repeated, using a blood pressure cuff about the lower thigh. With the superficial veins adequately obstructed, only enough dye was noted above the level of the cuff to indicate obstruction of the femoral vein (Fig. 5, *B*).

In view of the fact that the superficial veins were normal and were playing an important part in the collateral circulation of this extremity, it was decided that no surgical procedure was indicated on either the deep or superficial venous systems at that time. As an effort to relieve the symptom of pain, a lumbar sympathectomy was performed, and the postoperative result has been gratifying. After fourteen months, pain and sweating are absent, and ulceration has not recurred. Swelling has been effectively reduced, so that elastic stockings are necessary only during long periods of stationary dependency. Lumbar sympathectomy has been observed to be beneficial in cases of complete deep venous obstruction and to augment the benefits of a femoral ligation procedure in a few patients. This benefit has been attributed to improvement of arterial blood flow and overcoming associated vasospastic phenomena.[5]

These venograms again prove the value of individual case evaluation. Patients in whom complete deep venous obstruction continues to exist need not be subjected to femoral vein exploration and efforts may be directed toward more effective therapeutic procedures.

Case 4.—L. M. (No. 13536), a 50-year-old white farmer, received a gunshot wound of the left abdomen and thigh at the age of 26, and, thirteen years later, developed a posttraumatic aneurysm of the left femoral artery. The aneurysm was removed, together with segments of the femoral artery and vein. During the ensuing ten years, resultant varicosities increased in size and he was troubled with pain, tiring, edema, and ulceration.

Venograms revealed adequate filling of the deep veins to a level in the lower thigh with excellent collateral circulation via the greater saphenous vein, which exhibited apparently

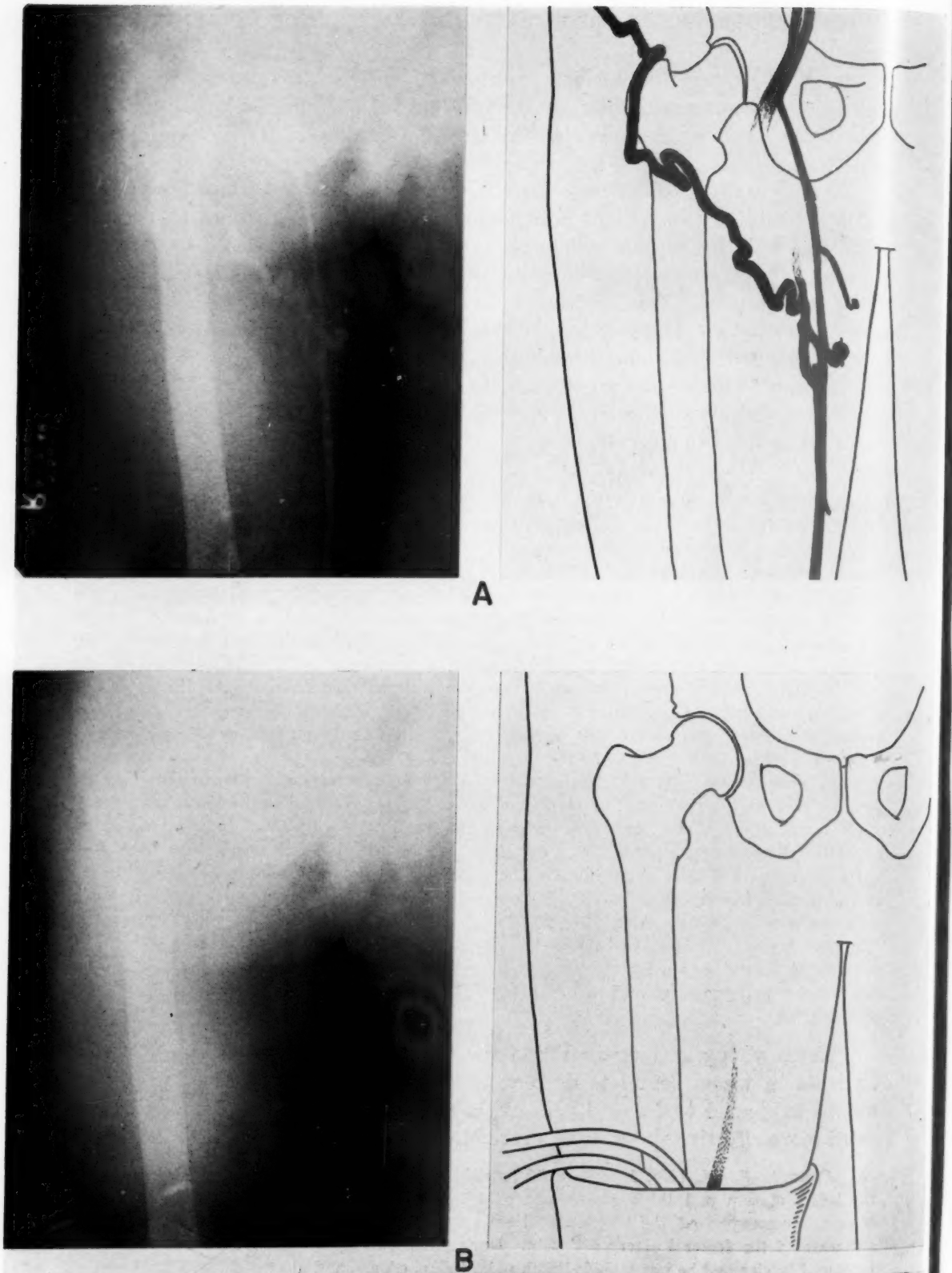

Fig. 5 (Case 3).—*A*, Venogram of thigh, tourniquet at ankle only. Complete deep venous obstruction with prominent collateral channels demonstrated. *B*, Repeat film with tourniquet at ankle and cuff about lower thigh, obliterating superficial collateral return, and confirming complete deep obstruction.

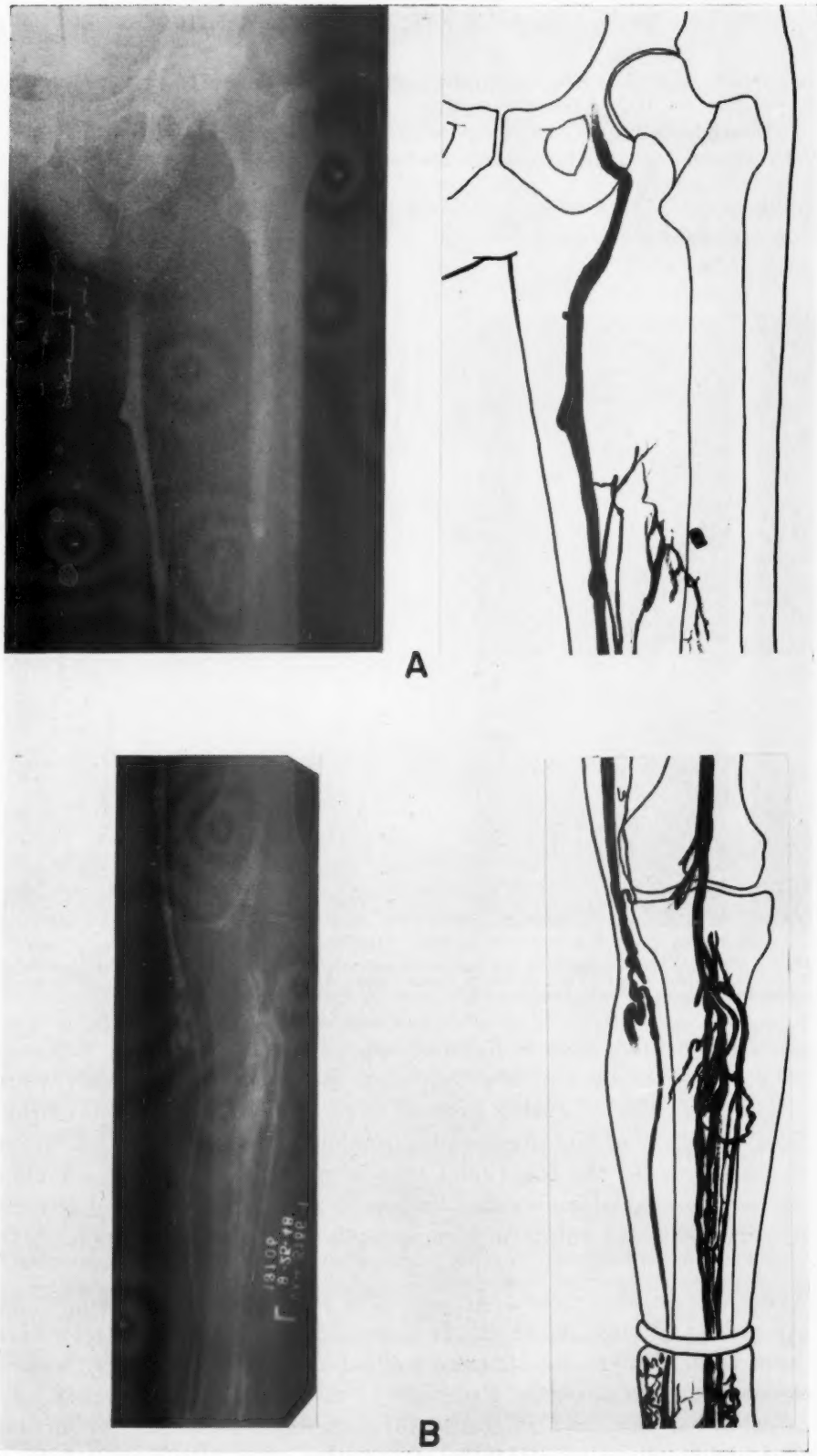

Fig. 6 (Case 4).—*A*, Venogram of thigh, tourniquet at ankle only. Complete deep venous obstruction in upper thigh with collateral circulation by way of greater saphenous vein. *B*, anteroposterior view of leg, tourniquet at ankle only. Dilated deep venous channels and filling of tortuous greater saphenous vein below the knee.

functional valves (Fig. 6). The incompetent communicating veins below the knee were believed responsible for the patient's symptoms. The saphenous vein distal to the knee was excised, and communicating veins were ligated. Subjective symptoms, swelling, and ulceration have not recurred during an eighteen-month follow-up period.

Venograms in this case demonstrated the patency of the tibial and popliteal veins and designated the level to which the saphenous vein could be excised with safety.

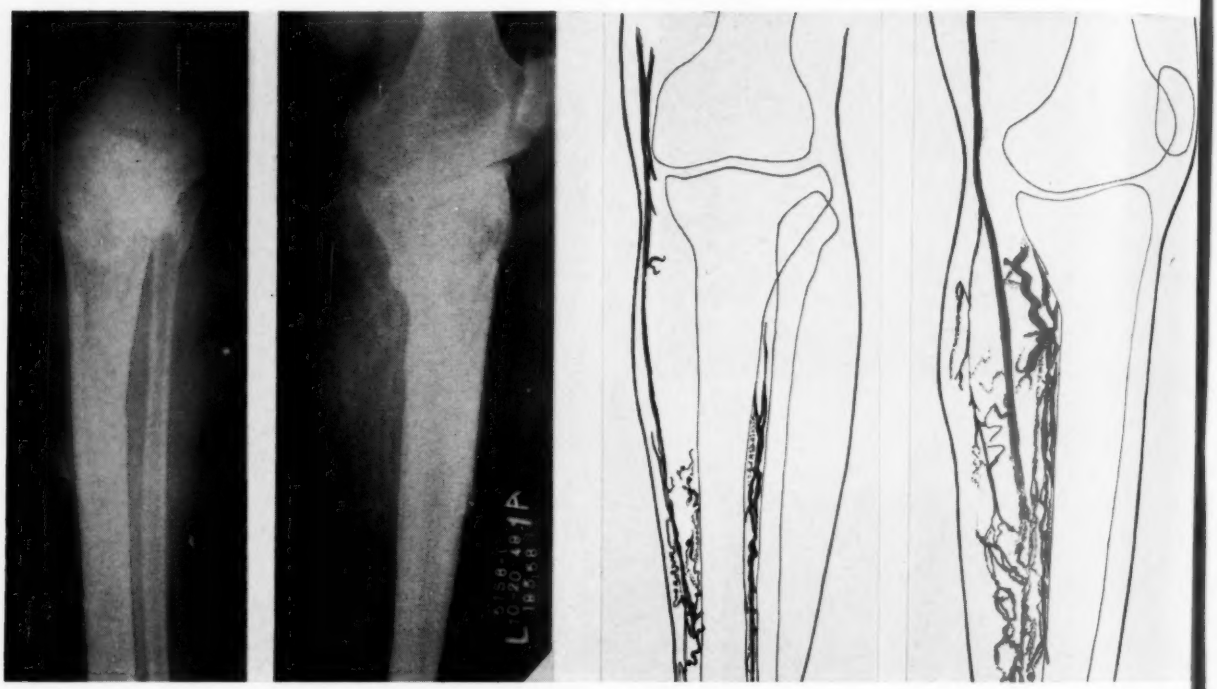

Fig. 7 (Case 5).—Venograms of leg (anteroposterior and lateral views), tourniquet at ankle only. Apparent obstruction of deep veins above the knee and filling of tortuous muscle branches and the greater saphenous vein.

Incomplete Obstruction or Recanalization.—The structure of vein walls is irreversibly changed by scarring following thrombophlebitis. Valves are destroyed either by the sclerosing process or by resultant dilatation of the vessel. Recanalization of the organized thrombus may follow. In either event, the vein is no longer the functional structure it was originally. A constant retrograde pressure, whenever the limb is dependent, is believed responsible for the persistent and refractory complications of the postphlebitic extremity.[1, 6]

Venograms in these cases demonstrate the shaggy irregular outline of the vein walls and multiple channels through which the dye may be diverted in such an area. Valves are almost always damaged in and below the location of the site of thrombosis. Frequently, recanalized deep veins are not demonstrable on the first injection for less resistance may be present in collateral channels and the dye by-passes the incomplete obstruction. The blood pressure cuff about the lower thigh effectively obliterates the super-

ficial collaterals and alters this pressure differential so that a greater concentration of dye then courses through such a recanalized vein.

CASE 5.—L. C. (No. 21374), a 54-year-old colored waiter, sustained a fracture of the left tibia in 1941, following treatment of which, in traction and cast, he began to note chronic swelling and ulceration of the left leg. All previous methods of conservative therapy had failed. Examination revealed swelling, brawny induration, and multiple areas of ulceration at the ankle.

Venograms confirmed the suspicion of recanalization. The anteroposterior and lateral views of the leg, after injection below the level of the tourniquet at the ankle, revealed prompt reflux of the dye from the deep to the superficial veins, with marked pooling in the tortuous muscle and superficial branches, and filling of the greater saphenous vein (Fig. 7). In the thigh, the filling of the saphenous progressed up to the point of its entrance into the common femoral vein, and with a tourniquet only at the ankle, the deep veins failed to fill (Fig. 8, *A*). It would not be difficult to assume, from this picture, that the patient still had deep venous obstruction, as in Case 3.

It was readily seen, however, after repeating the series using a blood pressure cuff about the lower thigh, that a shaggy-appearing superficial femoral vein and a collateral deep vein filled, and that the dye passed into the external iliac vein (Fig. 8, *B*). This was confirmatory evidence of previous thrombosis and subsequent recanalization—a finding that was verified at operation. A block removal of segments of the deep, superficial, and common femoral veins was carried out. Though the follow-up interval has been only four months, swelling has been minimal, ulceration has not recurred, and the patient has been able to return to his occupation.

The value of the blood pressure cuff technique is again exemplified by this case. The suggestion of complete deep venous obstruction was disproved and the demonstration of recanalization indicated the necessity for femoral vein excision.

CASE 6.—H. C. (No. 14712), a 49-year-old white man, sustained a crushing injury of the left ankle, resulting in multiple fractures and subsequent wound infection, while in the Navy in 1945. During hospitalization he developed thrombophlebitis, and following release from the service, with total disability, he suffered with constant ankle pain, swelling, and recurrent ulceration of the left leg. Amputation had been advised at another hospital.

A left lumbar sympathectomy with excision of ulcer and grafting, in February, 1948, afforded relief of pain, but these procedures were followed by persistence of swelling, brawny induration, and ulceration. The original venograms in November, 1948, revealed filling of the greater saphenous vein via incompetent communicating veins and suggested a complete femoral block above the level of the mid-thigh (Fig. 9). The saphenous vein was excised below the knee to the level of the ankle, and the ulcer healed temporarily. Following periods of limited dependency, however, edema and ulceration continued to recur. He returned to the hospital in October, 1949, with thrombophlebitis along the course of the greater saphenous vein in the thigh, and was successfully treated with heparin. Repeat venograms, one year after the first study, revealed conclusive evidence of an old thrombotic process of the common and superficial femoral veins with recanalization and prominent collateral circulation through the greater saphenous and a pudendal vein anastomosis to the right femoral vein (Fig. 10, *A*).

Exploration of the left femoral region was carried out and venographic findings were verified. A four-inch segment of the common femoral and adjacent superficial and deep femoral veins was removed. Valves within the specimen were scarred and withdrawn (Fig. 10, *B*). Injection of dye into the specimen revealed even more clearly the evidence of multiple channels through the diseased vein (Fig. 10, *C*). Microscopic sections demonstrated the recanalization process (Fig. 10, *D*).

Though only four months have elapsed, too brief a time for final evaluation of the last operative procedure, the patient's swelling has been considerably reduced. There has been no recurrence of ulcer, and he has remained symptomatically improved.

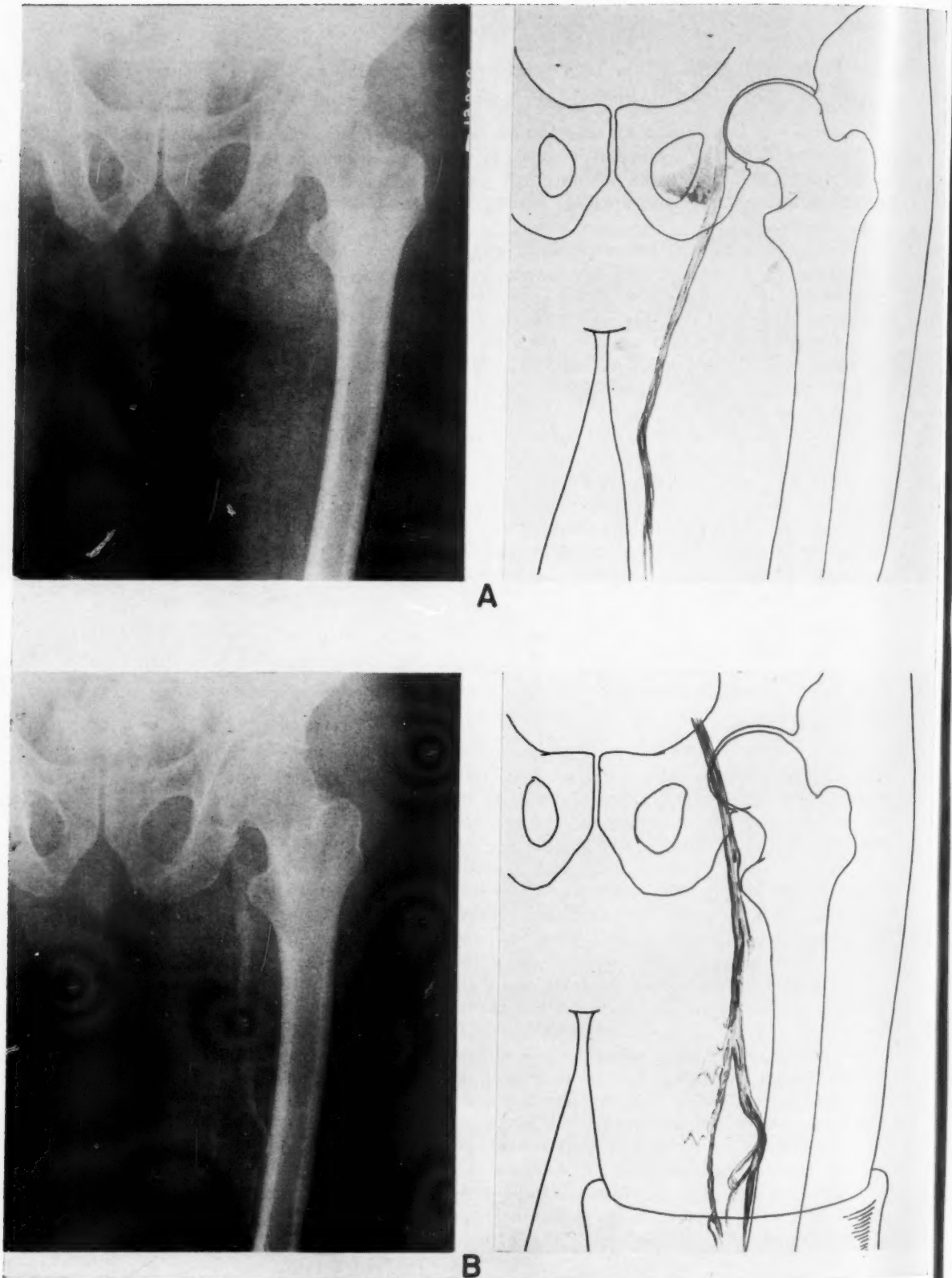

Fig. 8 (Case 5).—*A*, Venogram of thigh, tourniquet at ankle only. Apparent deep venous obstruction and collateral by way of greater saphenous vein. *B*, Repeat with tourniquet at ankle and cuff about lower thigh. Demonstration of recanalization of deep veins.

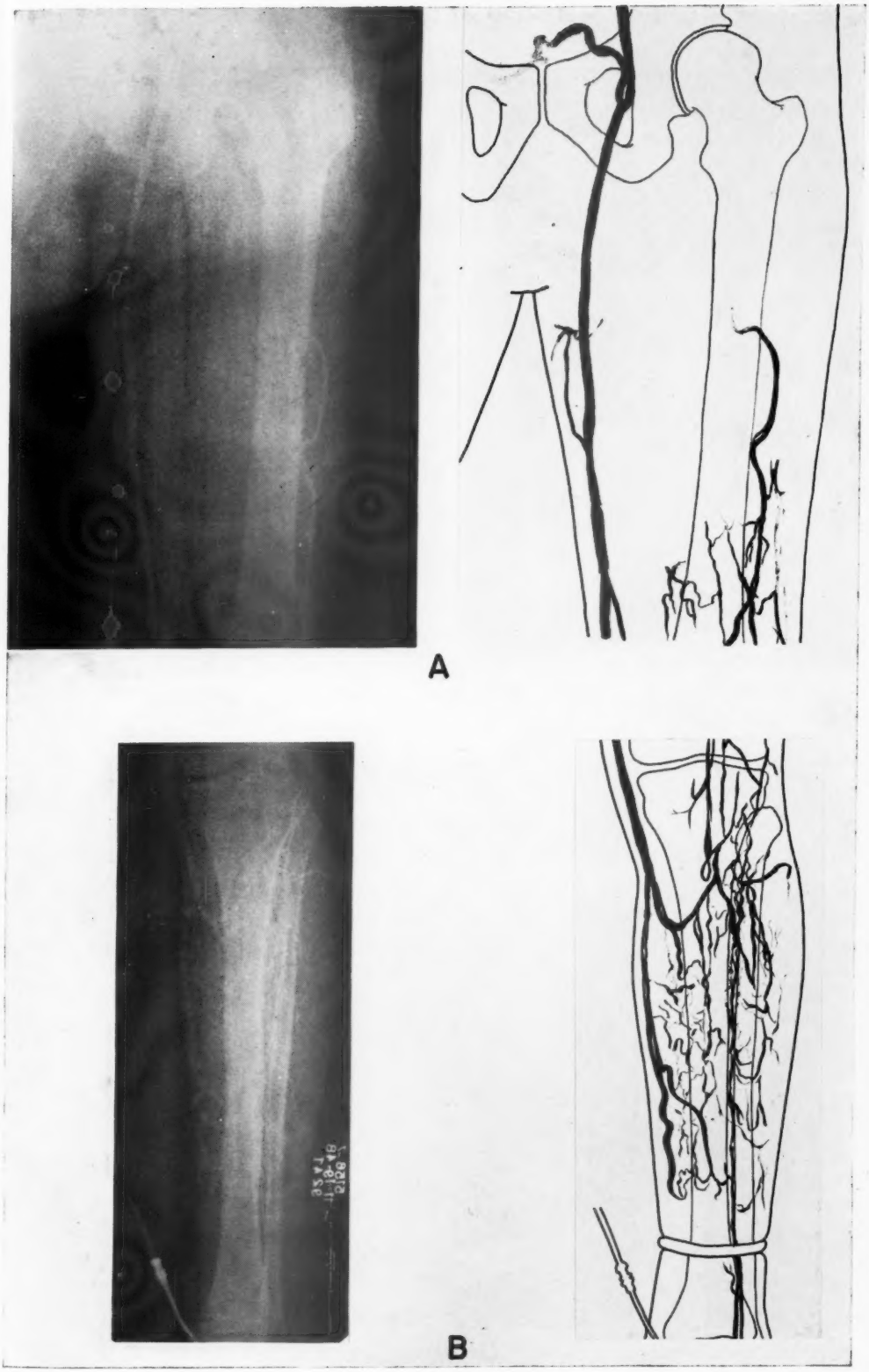

Fig. 9 (Case 6).—*A*, Venogram of thigh, tourniquet at ankle only. Complete deep venous obstruction and collateral circulation by way of greater saphenous vein. *B*, Venogram of leg, anteroposterior view. Normal deep channels replaced by a network of small veins and filling of greater saphenous vein by multiple communicating veins. Demonstration of static venous channels about ulcer area.

A

B

C

D

Fig. 10. (Case 6).—*A*, Venogram of thigh, a year later than Fig. 9. Demonstration of recanalization of deep veins. Prominent collateral circulation by way of greater saphenous and pudendal anastomosis to contralateral deep veins persists. *B*, Photograph of vein specimen. Pins indicate location of scarred, retracted valves. *C*, Vein specimen injected with dye to demonstrate multiple channels. *D*, Photomicrograph of cross section of recanalized vein.

This example of individualization of surgical procedures as they become necessary demonstrates the role that venograms have played in the final evaluation of the problem. It is believed that such individualization has led to the preservation of the extremity and to the rehabilitation of this patient.

DISCUSSION

Venograms have proved to be of practical application in the individual evaluation of disorders involving the deep veins of the lower extremity. Indications for this procedure have been limited to those cases in which a definite history of thrombosis is elicited or physical findings suggest sequelae of thrombosis that cannot be explained adequately on the basis of other pathologic entities.

The technique is not recommended for all problems of simple varicose veins, but is useful for study of those in which the etiology for the varicosities might be on the basis of complete or incomplete deep venous obstruction. Varicose vein problems which may have been previous surgical failures frequently can be enlightened by this study. Though not an expensive procedure when compared with other x-ray techniques, its use for cases other than those of questionable etiology entails needless patient expense and procedure. Though communicating veins with incompetent valves may be localized in this manner, it is unnecessary as a routine measure and may be unreliable in varicose vein examinations, as noted in Case 2.

The use of the Perthes test and wrapping the varicosed extremity with elastic bandages have long been acceptable methods of clinical evaluation of the deep venous circulation in anticipation of surgery for varicose veins. While these procedures are generally adequate, there are instances when they are not completely reliable. When questionable physical findings exist, venograms may provide confirmatory evidence of normal or abnormal deep veins. As an example, Fig. 11 shows a patient whose extremity had been firmly wrapped, foot to high thigh, with elastic bandages, for such a clinical test. The multiple tourniquet test had demonstrated incompetent greater saphenous and communicating veins, and Perthes' test was inconclusive. Venograms made with the firm elastic wrappings about the extremity demonstrated failure to collapse the superficial veins, with the greater portion of the dye returning by the saphenous system. The patient had not complained of symptoms of deep venous obstruction. The inference that superficial veins were occluded by the bandages and that patency of the deep veins did exist would have been unreliable in this instance. Venograms should be used more often in questionable cases instead of depending on the wrapping test.

When recanalization is proved to exist, venograms not only reveal the point at which the surgical attack should be directed, but, in addition, demonstrate those tributaries of the recanalized common femoral vein which have direct communication with veins below the knee. In four of the thirteen cases in which exploration was carried out, the deep leg veins were noted on venograms to have direct connection with the profunda femoris vein. In the

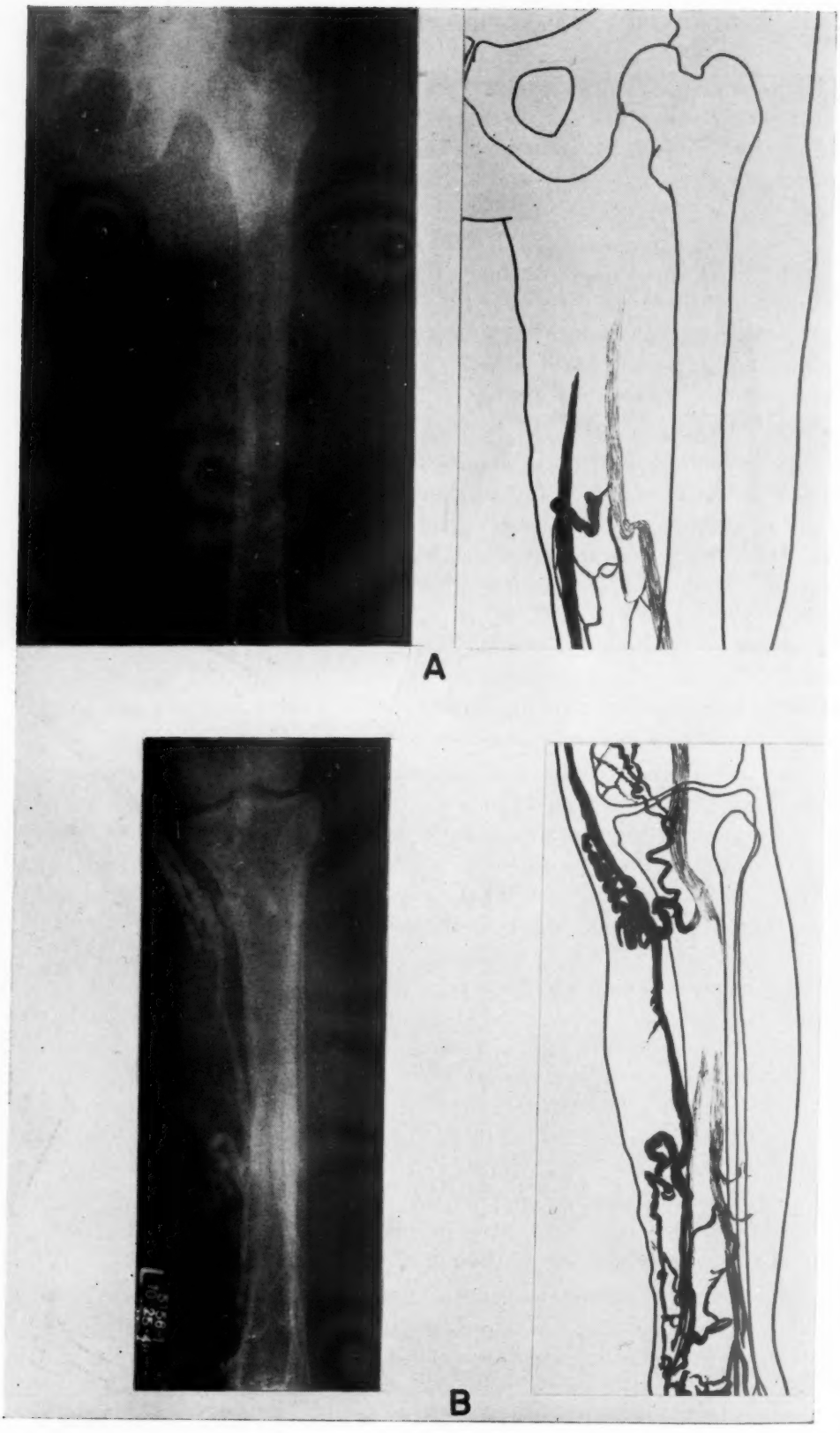

Fig. 11.—Venograms of thigh and leg. Demonstration of filling of greater saphenous system by incompetent communicating veins, despite firm elastic bandages from foot to high thigh and patient's recumbent position.

event that the profunda femoris is involved in the same pathologic process, interruption of the superficial femoral vein alone might not be expected to accomplish the anticipated cure.

Shumacker[6] and Luke[8] have made preoperative venograms by retrograde femoral vein injection. Bauer[2] and Sandegard[4] have reported similar injection techniques performed on the operating table at the time of exploration. The preoperative study as recommended by Shumacker seems more generally useful than the operative approach used by Bauer and Sandegard. While these procedures have value, it is believed that they cannot be as routinely informative as the ankle vein injection method described. Preoperative retrograde injection is not only exacting due to the depth of the venipuncture, but is even more difficult in the very cases in which information is most desired—the scarred, thick-walled, small-lumen vein. If the flow is halted at the first valve, existent pathology distal to that point may not be demonstrated. With the retrograde method, complete obstruction or recanalization above the injection point may be overlooked. Most important, information is not obtained regarding the total collateral circulation of the extremity.

Bauer[2] described a large group of patients who present signs and symptoms of the postphlebitic extremity, and in whom retrograde filling of the veins of the extremity occurs. Radiographically, the veins appear normal, and there is no evidence of recent or past inflammatory disease. He terms this group "idiopathic femoral insufficiency" and recommends ligation of the popliteal veins. However, both Shumacker[6] and Luke[8] have shown that a considerable number of individuals without signs or symptoms of disordered venous return show regurgitation by the retrograde method. A large group of patients have only severe varicosities, with edema and ulceration. Since retrograde filling occurs in normal extremities, it cannot be inferred that all of these patients showing reflux belong in the "idiopathic" group of Bauer. Widespread clinical experience has proved that many of these people may be cured by superficial venous surgery.

The retrograde route of injection appears most indicated in those patients with signs and symptoms of retrograde deep venous stasis, whose venograms are normal by dye injection at the ankle. In those in whom reflux is not noted on retrograde injection, treatment can be directed to removal of superficial pathology. If reflux filling does occur, the final decision will have to be based on clinical evaluation. Ligation of the popliteal or superficial femoral vein would appear indicated only in those cases in which the edema, induration, and ulceration seem disproportionate to the severity of the varicosities. Superficial venous surgery is done on all others and clinical response will serve as a guide to those few who may later need deep venous ligation.

We believe venograms performed with the dye injected into a foot or ankle vein provide valuable information regarding the superficial and deep veins of both the leg and the thigh. The method would seem more useful and informative than the retrograde approach in those cases with recanalization or residual complete femoral vein obstruction. More complete information is

obtained as to the site and type of pathology, the location, size, and course of collateral channels, and their proximal and distal connections. It enables rational selection of cases for ligation of the femoral and/or the popliteal veins, or removal of appropriate abnormal superficial veins.

SUMMARY

1. A new method of venography is described, which has been used effectively in the evaluation of seventy-five cases of venous disease of the lower extremity.

2. The technique, using 35 per cent Diodrast, provides a maximum of information with a minimum of procedure.

3. Information is obtained as to site and types of pathology, and location, size, and course of collateral channels.

4. Comparison is made with the retrograde femoral injection method, and the advantages of each are discussed.

5. A plan is described which enables individualization in the treatment of the postphlebitic extremity.

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DISCUSSION

DR. H. SHUMACKER.—I should like to congratulate Dr. Martin and Dr. McCleery for this new addition to the general technique of visualization of veins by radiopaque methods. I do think that we must keep in mind one fact, however, with regard to any venographic studies; namely, that the demonstration of patent channels in the recumbent position does not necessarily infer that those channels function to return blood toward the heart when the patient assumes the erect position. This is perfectly obvious, for example, from the fact that superficial varicose veins may be filled nicely in the recumbent position, but carry blood in the opposite direction when the patient stands.

With regard to the retrograde filling of the deep femoral system when dye is introduced into the proximal portion of that system with the limbs dependent, I should like to say that our associates in Indianapolis have been trying to establish some normal observations in people who do not have symptoms. Thus far it has been rather surprising to us to find that there are a considerable number of people without any symptoms at all in whom there is a reflux of Diodrast down the deep femoral vein when the legs are dependent. I suppose that the proper interpretation of this observation must be as follows: that it is possible for people to have incompetent valves in the deep femoral vein without symptomatology, just as we know it is possible for people to have for many years incompetent valves in the superficial veins without obvious symptoms.

I think that considerable time and much more study will be required before we are in a position to interpret with maximum usefulness observations of retrograde venography as well as some of these other techniques.

DR. R. S. McCLEERY (Closing).—I would like to say that the statement of Dr. Shumacker also has been affirmed by Luke seven years ago—that in patients with no symptoms whatever, reflux down the femoral vein may be demonstrated by the retrograde method. This detracts a great deal from the usefulness of this particular method.

We do feel, in trying to organize an approach to this problem, that those with normal venograms by our method should be studied by the retrograde method. In these patients with varicosities, edema, and ulceration on whom you do a retrograde injection, we feel that if reflux is not present, you can then direct your attention with certainty to the superficial veins.

In those patients who have reflux, but who have normal-appearing veins by our method, you should evaluate clinically the proportionate severity of the edema and ulceration in relation to the severity of the varicose veins. If the amount of edema, and so forth, is great and the varicosities are mild, we believe this may be a case of the idiopathic insufficiency of Bauer, and that deep ligation should be done. On the other hand, if the varicosities are severe clinically, we believe they should be attacked first and follow-up study of the results of superficial surgery will disclose the necessity of ligation of the deep veins in a small proportion of these cases.

THE SURGICAL TREATMENT OF INTRACRANIAL ANGIOMATOUS MALFORMATIONS

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ANGIOMATOUS malformations of intracranial location have long been known to exist, but have excited little surgical interest until recent years. Under various designations such as angioma venosum, angioma arteriole, arteriovenous aneurysm, cirsoid tumor, angioma plexiform, serpentine angioma, and aneurysmal angioma, they have been regarded as interesting clinical curisoities.

In the classical monograph by Cushing and Bailey[1] published in 1928, detailed descriptions of such lesions were made but with the admonition that surgical extirpation would be unthinkable. Likewise, Dandy[2] regarded them as being inoperable and recommended cerebral decompression combined with x-ray therapy.

Radical surgical removal of an intracranial angiomatous malformation was first successfully carried out by Olivecrona in 1932. Four years later, Bergstrand, Olivecrona, and Tonnis[3] reported five cases successfully treated. In 1946, Pilcher[4] reported three cases treated successfully by radical surgical removal, and urged that these lesions receive more serious surgical consideration. In 1948, Olivecrona and Riives[5] described their results in forty-three known cases with surgical removal in twenty-four. Except for the case mentioned by Penfield and Erickson[6] in 1941, in which a block removal of the angioma was carried out, there have been no other reports of surgical extirpation originating in this country. Trupp and Sachs[7] have recently recommended obliteration of the vascular channels that present on the surface by using long-continued, low coagulating current in light, stroking contact with the vessel wall.

In a recent publication, Norlen[8] of Sweden has reported ten instances of successful removal of such lesions with excellent results. Preoperative and postoperative angiograms leave no doubt as to the effectiveness of the complete surgical removal.

Spontaneous hemorrhage and convulsions are the clinical phenomena which occur most often in such cases. In addition, signs of increased intracranial pressure and focal neurologic signs may appear, depending upon the location of the lesion, but they are not necessarily characteristic of the disorder.

Spontaneous hemorrhage may occur in one of three general locations: subarachnoid, intraventricular, or intracerebral. In instances of intracerebral or subcortical hematoma of spontaneous origin, it is our belief that all except the arteriosclerotic type result from angiomatous malformations.

Convulsive phenomena due to intracranial angiomata offer no direct clue to the true nature of the lesion, but the presence of an angioma should be considered during the clinical investigation. In the present series, bruit was un-

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†Deceased.

common, being present in only two cases. Diagnostic intracranial calcification was not found in any case, although in three, intracranial calcification contributed to the accurate localization of the lesion.

There is little doubt that accuracy of diagnosis and a comprehensive preoperative study of the vascular lesion itself can be made only by cerebral angiography. This important diagnostic adjunct is now a simple and a relatively innocuous procedure. Furthermore, as shown by Norlen,[8] it can be used postoperatively as an accurate measure of determining the completeness of extirpation of the lesion. However, in five of the present series angiography was not performed because the nature of the lesion was unsuspected or because angiography was not in use at the time.

Anatomically, regardless of their location, all angiomatous malformations of the arteriovenous type consist of several large arterial trunks entering a central mass of tangled vessels, the angioma. Many large, thin-walled, friable venous channels constitute the outlet. Frequently these veins are found carrying blood of arterial color. Therefore, in spite of the large quantity of blood passing through the area, there is in actuality local tissue ischemia because of the absence of the normally interposed capillary bed. This may account for many of the focal neurological signs, rather than the actual mechanical presence of the angioma.

Microscopically, the vessels of the angioma vary greatly in size and shape. Many are thin-walled, consisting of little more than intima and a poorly developed media. Others show great proliferation of fibrous connective tissue in the media, but rarely is there proliferation of the intima. The surrounding cerebral tissue is often degenerated, showing excessive gliosis and fibrosis. Calcium deposits may be found within the vessel wall as well as in the extravascular tissues immediately adjacent.

The following eleven cases are representative of the various types of angiomatous malformations and illustrate the technical problems involved in their extirpation. Two patients in the series were reported on by Pilcher in 1946, but are included here as well for statistical completeness.

CASE REPORTS

CASE 1.—P. S., a 12-year-old white girl, entered Vanderbilt University Hospital March 27, 1941, one year after the onset of convulsive seizures. The first attack began with paresthesia in the right hand extending to the face and followed by clonic movements, also beginning in the right hand and gradually becoming generalized. During the next twelve months, there were similar attacks at intervals of about one month. Examination disclosed no abnormality except for a slight prominence in the left parietal area. X-ray examinations of the skull showed a circular line of calcification in the left frontal area which at first was thought to be a hydatid cyst. Exploration revealed an arteriovenous malformation emptying into the superior longitudinal sinus through a huge venous channel approximately 3 cm. in diameter. The lesion was removed after the arterial supply had been secured with silver clips. There was a transient postoperative aphasia and right hemiparesis which cleared up completely. During the nine years since her operation, she has continued to have occasional brief focal convulsive seizures at intervals of from one to six months. There have been no other symptoms and she has been able to complete her schoolwork.

CASE 2.—W. K., a 29-year-old white man, entered Vanderbilt University Hospital Jan. 29, 1943, six years following his first convulsive seizure. This attack was characterized

by rotation of the head to the right, followed by unconsciousness and clonic movements of the right arm and leg. Attacks of this type continued at intervals from one to three months for about two years and at intervals of about one year during the next four years. Transient episodes of paresthesia in the right arm occurring about once daily began four months before his admission to the hospital. Five months before admission he experienced a spontaneous subarachnoid hemorrhage from which he recovered in a period of ten days. During the next three months he developed mild motor aphasia.

Examination disclosed slight right hemiparesis with hyperreflexia and mild motor aphasia. In x-ray pictures of the skull, a small circular rim of calcification could be seen in the left parietal area surrounded by many small punctate calcifications. Exploration of the area revealed a large parietal arteriovenous malformation which was excised after occlusion of the arterial supply from the left middle cerebral artery. Following the operation, there was marked right hemiparesis and aphasia, both of which improved gradually over a period of several weeks. Slight spasticity of the right upper extremity, astereognosis, and agraphesthesia were still present two years following the operation. Occasional momentary paresthesias in the face and right hand were still present at this time.

CASE 3.—B. A., a 29-year-old white man, entered Vanderbilt University Hospital July 28, 1948, eight months after an acute illness characterized by sudden severe headache, stupor of four weeks' duration, aphasia, and right hemiparesis. Five months after the acute illness, he experienced a tonic, clonic convulsive seizure beginning in the right foot and spreading to become generalized. Two more similar attacks occurred during the next three months.

On examination, he appeared generally well, with mild right spastic hemiparesis, more marked in the face and arm than in the lower extremity, and mild expressive aphasia. The spinal fluid protein was 62 mg. per cent. A large cavity in the left frontal lobe lateral to the anterior horn of the left lateral ventricle was demonstrated in a pneumoencephalogram. Left frontal craniotomy revealed a large, thin-walled vein containing arterial blood and overlying a tangled subcortical mass of vessels about 3 cm. in diameter adjacent to the cyst of the left frontal lobe. This mass was removed after the arterial blood supply had been secured. Following the operation there was some improvement of speech and movements of the right side. Two convulsive seizures occurred during nine months following the operation.

CASE 4.—J. H., a 34-year-old white man, entered Vanderbilt University Hospital April 20, 1949, five days after a generalized convulsive seizure. The onset of this attack was not observed but no focal characteristics were noted by his family. He had experienced no previous convulsions, but about eight years earlier had noticed the onset of slight weakness in the left upper extremity; this weakness remained very slight. For about three years he had experienced occasional bifrontal headache and about two years before admission he noticed occasional episodes of paresthesia in the left upper extremity beginning in the hand and progressing up the arm. The findings of the initial examination were slight left facial weakness, generalized weakness of the left upper extremity with slight muscular atrophy in the hand, and very slight hyperreflexia and astereognosis and agraphesthesia in the left hand. At a subsequent examination, a loud bruit could be heard over the left parietal area. The pineal gland appeared to be slightly displaced to the left in anteroposterior x-ray studies and a faint area of flocculent calcification could be seen in the right parietal area. Exploration disclosed a very large arteriovenous malformation with numerous tortuous arterial channels and several large veins containing red arterial blood. The lesion lay in the sylvian fissure and because of the danger of a crippling paresis, it was not removed. During the seven months following the operation, no further convulsive attacks occurred. His headaches were relieved but the neurological findings remained unchanged.

CASE 5.—R. M., a 32-year-old housewife, entered Vanderbilt University Hospital Nov. 27, 1948, five days following a spontaneous subarachnoid hemorrhage accompanied by severe headache, stiff neck, and stupor. Examination disclosed bilateral early papilledema, stiffness

of the neck, and right Babinski sign. The spinal fluid was grossly bloody. Arteriograms demonstrated a dense, tangled network of vessels in the distribution of the left anterior cerebral artery. One month after the onset of symptoms, left frontal lobectomy was carried out with ligation of branches of the left anterior cerebral and middle cerebral arteries entering the vascular malformation. There was severe bleeding from blood vessels entering the lesion before they could be secured. Convalescence was slow, with residual aphasia, right hemiparesis, and intellectual impairment still present ten months following treatment.

CASE 6.—M. S., a 7-year-old white girl, was admitted to Vanderbilt University Hospital June 24, 1947, because of headache, prominence of the left eye, and subconjunctival hemorrhage. There was papilledema on the left with slight exophthalmos. Roentgen therapy totaling 2,400 roentgen units was administered over the left frontal and temporal areas at this time. Seventeen months later a spontaneous subarachnoid hemorrhage occurred. At this time there was bilateral papilledema. One month later, a second subarachnoid hemorrhage occurred. Left carotid arteriograms made after the first attack were negative. A pneumoencephalogram following the second attack showed upward displacement of the inferior horn of the left lateral ventricle. A small arteriovenous angioma having a single large venous channel was extirpated. Six months later, right hemiparesis and aphasia suddenly developed, becoming marked over a period of five days. There was no headache or subarachnoid hemorrhage. Six months later this had improved considerably although moderate spasticity, partial right homonymous hemianopia, and slight aphasia were still present.

CASE 7.—F. T., a 26-year-old white man, was admitted to Vanderbilt University Hospital Sept. 13, 1948, ten months following an acute illness when he was found by his father in a generalized clonic, convulsive seizure. After he recovered consciousness, he complained of severe occipital and bitemporal headache and was unable to move the left arm and leg. He was found to have bloody spinal fluid. In the course of twenty-four hours the left hemiparesis cleared up, but he continued to complain of intermittent headache for about six weeks. Five months later, a second convulsion occurred, beginning in the left side of the face and spreading to involve the entire left side of the body. Two more similar attacks occurred during the next five months. No abnormal findings were present at the initial examination. A cerebral arteriogram showed a large arteriovenous plexus in the right posterior frontal area. He was given x-ray therapy totaling 2,200 roentgen units. Two weeks after the completion of x-ray therapy, he had one more convulsive attack but during the next nine months there were no further seizures or symptoms of any kind.

CASE 8.—E. A., a 24-year-old white man, entered Vanderbilt University Hospital Sept. 30, 1947, six days following a spontaneous subarachnoid hemorrhage. There were no abnormal neurological signs. A pneumoencephalogram was negative. A right carotid arteriogram demonstrated a small arteriovenous plexus in the right posterior parietal area. The lesion was exposed and removed although great difficulty in controlling the arterial blood supply was encountered. Convalescence was uncomplicated except for partial left homonymous hemianopia. Four months after the operation, he first experienced a transient feeling of numbness in the left arm and leg lasting about three minutes. Attacks of this type occurred at intervals of about four weeks for the next year, but only one occurred during the following year.

CASE 9.—H. B., a 32-year-old white man, was admitted to the Thayer Veterans Administration Hospital June 26, 1948, with a history of periodic attacks of unconsciousness, dizziness, and headache of three years' duration, and one attack of spontaneous subarachnoid hemorrhage. Physical and neurological examinations were negative. X-ray examination of the skull was negative. Arteriograms revealed a large angiomatous malformation in the left parietal region. At operation, the feeder vessels were all secured, clipped, and the angiomatous mass was totally removed. Postoperative course was uncomplicated except for a partial paralysis on the right with some aphasia. This showed progressive improvement. Follow-up studies have indicated continued improvement. An occasional convulsive seizure is being controlled by anticonvulsant medication.

CASE 10.—I. C., a 40-year-old white man, was admitted to the Thayer Veterans Administration Hospital Oct. 29, 1948, with a history of a subarachnoid hemorrhage in 1945. He has since noted a continous bruit, which is heard on the left side, and increasing headache and dizziness. For three years he had had increasingly frequent convulsive seizures. A

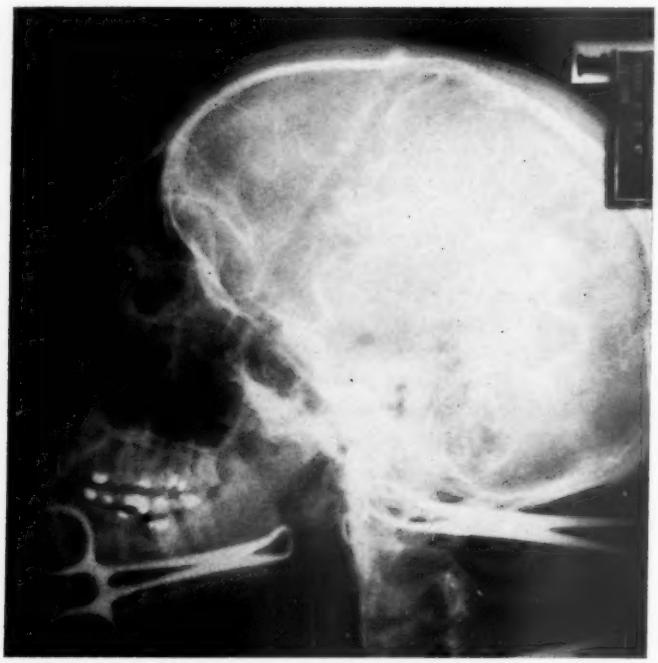

Fig. 1 (Case 8).—Angiogram demonstrating angiomatous lesion of right parietal area.

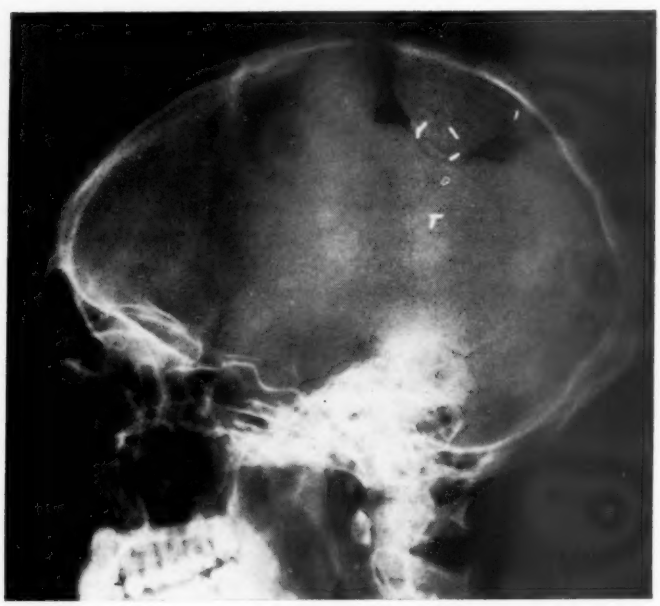

Fig. 2 (Case 8).—Postoperative x-ray picture showing clips on the major feeder vessels.

second attack of spontaneous subarachnoid hemorrhage occurred one year following the first. Neurological examination was negative except for the presence of a loud machinery-like bruit which was heard over the left side of the head. The patient lost consciousness im-

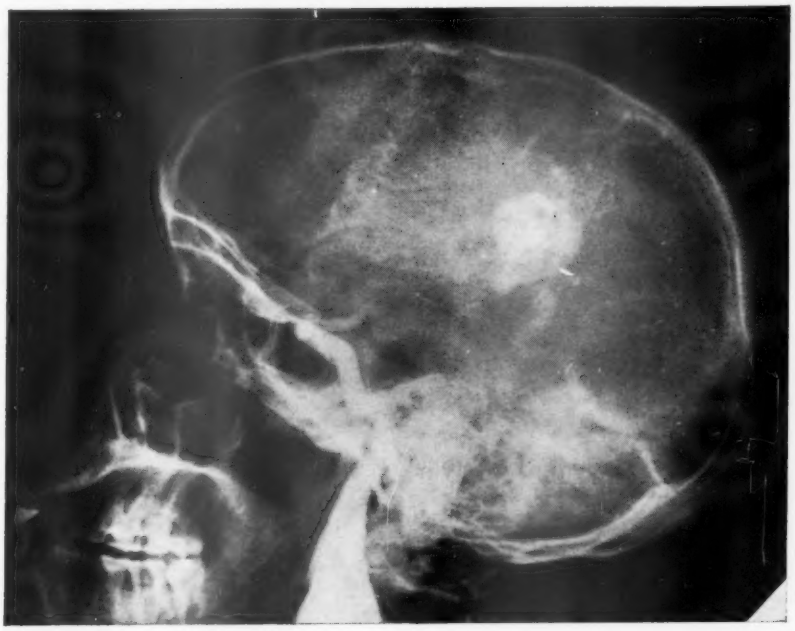

Fig. 3 (Case 9).—Angiomatous lesion of left parietal area demonstrated by angiography.

Fig. 4 (Case 9).—Postoperative x-ray picture. Hemostatic clips on feeder vessels.

mediately on compression of the left common carotid for a period of three seconds during which time the bruit was diminished. Arteriograms revealed the presence of a huge angiomatous malformation occupying the major posterior portion of the left cerebral hemisphere, principally in the temporal and parietal areas. This was thought to be inoperable and was given x-ray treatment, after which the bruit was diminished and the patient was symptomatically improved. Arteriograms performed approximately one year later were unchanged. Ventriculograms at this time showed a shift of the ventricular system to the right side. The patient's condition had remained slightly improved following the x-ray therapy. Because of this poor result of conservative management, the possibility of removing the lesion was again reviewed in January, 1950. An anteroposterior arteriogram which had not been performed previously revealed that the lesion extended from the surface of the left hemisphere throughout the entire thickness of the hemisphere to the midline. Since the common carotid or internal carotid artery could not be occluded due to the patient's intolerance, it would seem that this lesion was definitely inoperable and that surgery would only result in permanent aphasia and paralysis. Consequently his treatment is remaining purely symptomatic with anticonvulsant therapy.

CASE 11.—J. F., a 22-year-old white man was admitted to the Thayer Veterans Administration Hospital on April 17, 1948, for study regarding possible brain tumor. There was on admission noticeable weakness in the right hand with poor coordination of the right extremity. There was some associated diminution in sensory perception on the entire right side of the body. The initial impression was left frontal lobe tumor. Ventriculography was not entirely satisfactory and decision regarding operation was deferred to allow more time for observation. Four months later, the patient returned for examination and at this time there was some very definite early papilledema present. The ventriculogram previously performed had been made through anterior burr holes and on the second admission to the hospital posterior parietal burr holes were made to carry out a ventricular air injection. Under a local anesthetic this was carried out and when the ventricular needle was inserted into the left side, there was an immediate forceful and continued gush of arterial blood through the cannula. The patient immediately showed signs of collapse, and, since there was no method of controlling this hemorrhage, he was immediately and rapidly anesthetized and a large left temporoparietal osteoplastic flap was turned down. The brain was extremely tight but presented no abnormalities on the surface. A cortical incision was made and carried down to the point where the ventricular needle had been inserted. As soon as the ependyma of the left lateral ventricle was opened, there was a profuse and massive escape of blood from the ventricular system with some immediate improvement of the patient's condition. It was then seen that the entire posterior portion of the left lateral ventricle was filled with a large angiomatous tangle of very large, friable, and thin-walled vessels, from which there was brisk arterial bleeding. The lesion was removed rapidly after the large feeder vessels had been clipped. Despite a transfusion of 3,500 c.c., breathing ceased as the operation was completed.

DISCUSSION

The surgical attack on intracranial angiomatous malformations should be planned carefully in advance, but as Pilcher[9] previously emphasized, the surgeon must have the courage to abandon his attempts to remove the lesion should it prove obviously beyond the scope of successful extirpation. A satisfactory demonstration of the angioma by arteriography as a preliminary study is of the greatest importance. An adequate surgical exposure of the lesion and its tributaries must be obtained by utilizing a generous, well-placed osteoplastic flap. As the peripheral feeder vessels are followed into the cerebral tissue to the central mass, control of bleeding will be assured by occlusion of the arterial tributaries as they are encountered. The angioma should never be attacked

directly for profuse and almost uncontrollable hemorrhage from the intact tributaries will result. After occlusion of the arterial radicals, the venous tributaries are then identified, occluded and the lesion removed. Lobectomy as an alternative plan of removal may be used when the angioma is located in the frontal or occipital lobe.

SUMMARY

Eleven cases of intracranial angiomatous malformation have been presented. It is recommended that all such cases receive a complete and comprehensive diagnostic study. Surgical removal should be seriously entertained if the lesion is accessible and can be removed without profound and permanent neurologic impairment, even though the operative risk may be great.

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DISCUSSION

DR. RAY.—With the wider use of cerebral angiography, all neurosurgical clinics are finding more and more of these cases. I think that we shall come to realize that the cases will fall into those that have relatively small anomalies which lie in a relatively remote part of the hemisphere, and those that are very large and lie in the central part, the latter being inoperable, the others possibly operable.

It is quite challenging to attempt to remove one of these lesions, and there is no doubt but that there is great risk in tackling an anomaly of this kind under the best of circumstances.

We must consider the indications for operation and what we can expect as a result. The dangers to a patient who has such a lesion are these: convulsive seizure, paralysis, subarachnoid hemorrhage. We do not possess very good statistics which tell us how commonly these subarachnoid hemorrhages occur, at least fatally. If we knew that, then we could perhaps talk a little more intelligently about how useful a risk of operation would be.

As far as the paralyses are concerned, a lesion which will produce paralysis of itself is one that probably in its removal might produce more paralysis.

The removal of these lesions, if they have been causing convulsions, does not necessarily result in the cessation of convulsions, as has already been pointed out.

So that at best what we can offer these patients is a possibility of reducing convulsive seizures and a protection against their having a fatal hemorrhage.

Until we have a little better evidence on how important these things are, we are still in the formative period of our thinking.

COMPLICATIONS FOLLOWING SUBTOTAL GASTRIC RESECTIONS PERFORMED SINCE JUNE, 1944, FOR PEPTIC ULCER IN 132 PATIENTS

Comparison With Complications Following Vagotomy in 138 Patients

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SELDOM in the history of surgery for intractable peptic ulcer has there been general agreement among surgeons concerning technique or results. Neither has there been agreement concerning relative importance of acid-pepsin, hypermotility, and other local factors as cause of ulcer, some favoring a concept of etiology in terms of cephalic-vagus influences and others in terms of chemical or antrum-gastrin digestive factors. As the history of development of techniques and of physiologic basis for operations is reviewed, as by Mayo[1] and others in excellent articles, it is evident that from the start drainage of the stomach by gastrojejunostomy has been almost uniformly used alone or as part of popular operations. Because of this and since in our experience obstruction of the outlet of the stomach by scar tissue, spasm, or dysfunction of the pyloric sphincter is a major factor in persistence or frequent recurrence of ulcer, it seems evident that gastrojejunostomy in itself is an important surgical treatment.

Wolfler, in 1881, is commonly credited with introduction of gastroenterostomy, and this procedure remained popular for 50 years among most surgeons and continues as the preferred procedure for ulcer in certain selected cases by a few, including Balfour,[2] Walters,[3] Walton,[4] Sanders,[5] and Gardner and Hart.[6] Addition of resection of the antrum or antrum and media of the stomach to drainage by gastroenterostomy (Billroth I and II, Pólya, Hofmeister, and so on) was recommended by Haberer,[7] in 1920, and by Berg,[8] in 1928. Though at first strongly opposed, resection has gradually become the procedure now preferred by most surgeons. Demonstration by Dragstedt and Schafer[9] in 1945 that vagotomy alone frequently healed ulcer gave early encouragement that a neurophysiologic approach without gastroenterostomy might produce results comparing favorably with those of resection-gastroenterostomy. However, we[10] found after several years of experience that although results remained excellent in a majority of the patients with this procedure, complications including occurrence of retention symptoms and recurrence of ulcer necessitated frequent secondary gastroenterostomy. It was therefore recommended that vagotomy alone be abandoned in favor of transabdominal vagotomy with gastrojejunostomy.

This study was aided by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Grant.

We are indebted to members of the surgical resident staff and of the senior surgical and medical staff who have made available much of the material studied.

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Both resection-enterostomy and vagotomy-enterostomy as used, depending upon preference, by various surgeons for their patients requiring operation yield an encouraging incidence of good clinical results. Each also yields an incidence of complications. Final evaluation of relative merit of one or the other of these procedures will require many years and will probably be determined by incidence of occurrence and the success in management of these complications.

Being familiar after 5 years of study with occurrence and treatment of complications following vagotomy,[11] it seemed advisable at this time that we attempt an evaluation of those following resection. Examination of the literature revealed that of the surgeons originally studying vagotomy Dragstedt[12] now seldom employs vagotomy alone but continues routinely with vagotomy and posterior gastroenterostomy. Moore,[13] experiencing difficulty as we did with vagotomy alone, has returned to subtotal gastric resection rather than adopting for study vagotomy with gastroenterostomy. Walters[14] experienced difficulties particularly when combining transabdominal vagotomy with local resection of ulcer. Many later observers using vagotomy with gastroenterostomy have reported favorable results but with few exceptions they, like ourselves and the aforementioned authors, changed at one time from resection to vagotomy and thus could base any evaluation only upon late results of resection and early results of vagotomy. It has been our experience that the early complications after vagotomy can be troublesome and best results are seen in patients followed a year or more. To our knowledge only one group of investigators, Crile, Jones, and Davis,[15] has compared results in a contemporary series of resections and vagotomies. They describe better results in 87 patients treated by vagotomy with gastroenterostomy than in another 87 patients, 67 of whom had resection and 20 gastroenterostomy alone.

In our hospital some staff surgeons[6] prefer resection as their usual treatment and one of us[10, 11] prefers vagotomy-gastroenterostomy. Since June, 1944, when the latter procedure was begun, there have been in this hospital and in relatively similar groups of patients 132 resections and 135 vagotomies up to June of 1949. Of the patients originally treated by vagotomy alone there remain 37 who have not since required secondary gastroenterostomy. Present results in the vagotomy series were determined and presented as an exhibit before the Southern Medical Association in November, 1949. Similarly presented were results in the resection group.

Recognizing that we have not been in day-to-day contact with many of the resection patients, it is nevertheless thought worth-while that our interpretation of results in this group as determined by detailed record study, questionnaires identical with those sent to vagotomy patients, and re-examination of some of the resection patients should be presented. As with study and reports concerning vagotomy, emphasis will be placed upon evaluation of complications.

MATERIAL AND METHOD OF STUDY

The 132 subtotal gastric resections were performed for duodenal ulcer in 81 patients, for benign gastric ulcer in 39, for uncomplicated marginal ulcer in 4, for gastrocolic fistula complicating marginal ulcer in 3, and for duodenal and an associated gastric ulcer in 5. Of the 39 gastric ulcers, 23 were along the lesser curvature, 6 were at the channel of the pyloric sphincter, 3 were on the greater curvature, and 6 were in the posterior wall of the antrum. The remaining gastric ulcer diagnosed roentgenologically and treated medically before surgery was not located at operation, pathologic report being gastritis. Of the 81 patients with duodenal ulcer, 60 were male and 21 female. Similarly, of 39 with gastric ulcer 30 were male and 9 female. Of the 81 patients with duodenal ulcer, 63 were white, 14 Negro, and 4 Indian. Of 39 with gastric ulcer, 33 were white and 6 Negro. The average age at the time of operation of the 81 patients with duodenal ulcer was 46.5 years; and of those with gastric ulcer, 50.5 years. Average age of the whole resection group was 47.8 years. The average age of the 138 patients in the vagotomy series to be compared was at the time of operation 42.7 years.

Hospital records of each of these patients were examined to evaluate condition of patients before surgery, findings during operation, technique employed, and also results immediately after operation, during return visits to the clinic, and during readmissions when these occurred. Each record was summarized using a standard work sheet. This record study was supplemented by questionnaires mailed to each patient or completed during return visits. Present status was determined in all but 10 patients, these not being located. Since study of hospital records is complete and for the most part based upon objective data, results of this study will be presented first and results dependent upon statements of patients as obtained by questionnaire or by interview second.

RESULTS OF RECORD STUDY

Ulcer History.—Histories of 81 patients with duodenal ulcer recorded that before resection 38 had had bleeding evidenced by tarry stools and of these 33 had hematemesis. There had been several recurrences of bleeding in 17. In 3 bleeding was massive and continuing at the time of operation. Forty-eight patients, because of history of repeated vomiting, roentgenologic evidence of retention of barium, or gastric residual determined by aspiration, were considered as having obstruction. Fifty-six patients described troublesome pain and in 18 of these pain was continuous or intractable. Previous operations for complications or symptoms of duodenal ulcer were closure of perforation 14 times in 8 patients, appendectomy in 3, cholecystectomy in 1, and Finney pyloroplasty in 1. The major indication for surgery was uncontrolled bleeding in 3 patients, recurrent bleeding in 6, obstruction and pain in 38, intractable pain in 18, recurrent bleeding and obstruction in 11, and possibility of maligancy in 5 in whom the duodenal ulcers were not localized or recognized by roentgenologic examination or gastroscopy.

Histories of the 39 patients with gastric ulcer described bleeding evidenced by tarry stools in 22 and bleeding evidenced by hematemesis and melena in 12. There had been several recurrences in 8, but in none was there uncontrollable or persistent hemorrhage. Symptoms of obstruction were described in 6 and 11 had intractable pain at the time of operation. One of these patients had had a vagotomy without gastroenterostomy 5 months before resection.

Histories of the 4 patients with marginal ulcer described recurrent serious bleeding in each. Those of the 3 with gastrocolic fistula described diarrhea and marked weight loss. One also had bleeding. Operations preceding marginal ulcer and gastrocolic fistula were in each instance gastrojejunostomy. Histories of the 5 patients each with a duodenal and a gastric ulcer described pain and obstruction. Of the 132 patients with duodenal, gastric, or stoma ulcer 89 had low economic or ward status.

Operative Procedure.—Procedure employed for resection included removal of 50 to 80 per cent of the stomach and anastomosis of the jejunum to the remainder of the fundus. This anastomosis was made in 117 patients by bringing the loop of jejunum anterior to the colon and in 15 by bringing it through the transverse mesocolon posterior to the colon. Procedure elected for exclusion or closure of the duodenum in the 81 patients resected for duodenal ulcer was exclusion using Bancroft's modification of the Finsterer operation in 28, removal of the ulcer and suture of the duodenum in 28, and closure of the duodenum proximal to the ulcer without its removal in 24. In each of the 39 patients with gastric ulcer the lesion was removed and the duodenum was divided beyond the pylorus and closed by suture. In addition to subtotal gastric resection, appendectomy was performed in 7 patients, cholecystectomy in 3, repair of diaphragmatic hernia in 1, repair of a paraduodenal hernia in 1, splenectomy in 1, and in another, resection of the head of the pancreas on a presumptive but erroneous diagnosis of carcinoma. Division of the common duct during subtotal resection in another patient necessitated choledochoduodenostomy.

Procedures elected for repair of the jejunum in 3 of the 4 patients with marginal ulcer were resection of the site of the stroma ulcer with end-to-end anastomosis in 2 and lateral suture in another. The fourth patient had a stoma ulcer of the duodenum following a Billroth I resection. The ulcer was excised with suture of the duodenal stump followed by subtotal resection and antecolic gastrojejunostomy.

Procedure for repair of gastrocolic fistula in 1 patient was resection of the involved colon with primary end-to-end anastomosis, suture of the opening in the jejunum, and subtotal resection with anterior gastrojejunostomy. In the other 2, operation was closure of the opening in the colon and in the jejunum by transverse suture and subtotal resection with antecolic gastrojejunostomy.

Procedure employed in the 5 patients having both gastric and duodenal ulcer was in each instance resection of the gastric ulcer. The duodenal ulcer

together with a portion of the antrum was excluded in 2 patients. In a third the ulcer was left in place distal to closure of the duodenum. In a fourth the ulcer was removed and the duodenum closed. The fifth was the patient in whom the duodenal ulcer was excised together with the head of the pancreas, pancreatoduodenal resection being performed with an erroneous diagnosis of malignancy.

Operative Mortality.—Seven of the 132 resected patients died of immediate complications following surgery and 2 died late after surgery. Two of the deaths directly following surgery occurred among the 3 patients resected as an emergency measure during continuing massive bleeding and are not included in our evaluation of mortality rate with resection for comparison with that of vagotomy (Table I). They are included in this table as deaths from all related causes. Exclusion of these 2 patients leaves 5 deaths from immediate complications or a mortality rate of 3.9 per cent. One of the 5 deaths occurred from coronary thrombosis, and another from pulmonary embolus. These 2 resections had been performed for gastric ulcer. The remaining 3 occurred following operation for duodenal ulcer associated with an active inflammatory process or extensive scar. In 1 patient the ulcer was entered during release of adhesions and closed without removal. Generalized peritonitis followed and caused death. In the second the duodenal ulcer was removed but the patient became jaundiced 4 days after resection and a pancreatic fistula developed. A second operation was performed 7 days after operation and drains were inserted to the pancreas. External drainage of bile occurred 15 days later. After another 35 days a third operation was performed for repair of the injured common duct. Death from bile peritonitis occurred the fifth day after this operation. The third death occurred following removal of a densely scarred duodenal ulcer with an inadvertent severance of the common duct which was recognized during operation and repaired. Thrombophlebitis and pneumonia developed and the gastroenterostomy stoma functioned poorly. Ascites was evident 29 days later and progressively increased. In spite of therapy, death occurred 3 months later. Though autopsy was not obtained, thrombosis of the portal vein was suspected. The liver had been normal at the time of operation and jaundice did not develop afterward.

Two additional patients died late after resection, though surviving operation without immediate major complication. Since they died of causes not directly related to conventional subtotal resection, they are not included in the mortality statistics for comparison with those of vagotomy but are listed as deaths from all related causes, Table I. One of these 2 patients had bilateral pulmonary tuberculosis and developed atelectasis, azotemia, and diarrhea immediately after subtotal resection for stoma ulcer but recovered and left the hospital 24 days after operation. Five weeks afterward an abdominal fistula opened, the sputum became positive for tuberculosis, and he died 5 months later. The other patient is the one who had resection of the head of the pancreas and duodenum along with the partial gastrectomy for a duodenal

TABLE I. OPERATIVE MORTALITY AND INCIDENCE OF COMPLICATIONS DURING FIVE YEARS

	SUBTOTAL GASTRIC RESECTION (132 PATIENTS, 155 OPERATIONS) (PER CENT)	VAGOTOMY WITH OR WITHOUT GASTROENTEROSTOMY (135 PATIENTS, 159 OPERATIONS) (PER CENT)
Comparable patient mortality rate	3.9	0.7
Deaths during 5 years from this and related causes	6.9	1.5

	RESECTION (132 PATIENTS) (PER CENT)	VAGOTOMY WITH GASTRO-ENTEROSTOMY* (81 PATIENTS) (PER CENT)	VAGOTOMY ALONE (56 PATIENTS) (PER CENT)
Serious, nonfatal complications	15.9	7.4	26.8
Patients requiring secondary operation (not for ulcer)	15.1	6.2	29.4
Probable recurrence	5.3	1.2†	7.1
Possible recurrence by any suggestive symptom or finding	9.2	2.5	12.5
Operations for recurrence	2.3	0.0	7.1

*Includes all vagotomies with primary or secondary drainage or done for stoma ulcer following previous gastroenterostomy.

†One patient with persistence of stoma ulcer following a probable incomplete vagotomy as judged by high acid in an insulin test.

and a gastric ulcer with a mistaken diagnosis of carcinoma. Two and one-half years later he reported by questionnaire that his nutritional state was fair and bowel habits normal though he was not able to work because of rheumatism. Four years after operation, however, steatorrhea developed and weight loss, edema, and ascites gradually increased during 9 months, progressing in spite of treatment in the hospital and at home, until death occurred.

Of the original 132 patients, therefore, 123 remain for consideration of results of resection and incidence of recurrence of ulcer.

Nonfatal Operative Complications.—Of the 123 patients now living 35 survived postoperative complications. These were generalized peritonitis in 1, subhepatic abscess in 3, subdiaphragmatic abscess in 1, other intra-abdominal abscesses requiring drainage in 3, lung abscess in 2, pancreatic fistula in 1, and exsanguinating postoperative hemorrhage in 1. Wound disruption occurred in 9. Altogether there were 21 serious complications, 15.9 per cent (Table I). Troublesome, though temporary, malfunction of the gastroenterostomy stoma occurred in 11. Three patients 2, 4, and 7 months following subtotal resection were treated by operation for intestinal obstruction. Altogether, 20 secondary operations were required for these complications, 15.1 per cent (Table I).

Postoperative Stay in Hospital.—Although many of the 125 patients discharged following resection were able to leave the hospital 8 or 10 days after operation, the average postoperative hospital stay was 17.4 days.

Recurrence of Ulcer.—According to hospital records, 7 patients developed recurrence requiring hospitalization for medical or surgical treatment, 5.3 per cent (Table I). Twelve others described ulcerlike symptoms, 9.2 per cent (Table I). These will be discussed separately.

Medical treatment alone was employed for probable or possible recurrence of ulcer in 4 of these 7 patients. One developed severe epigastric pain

7½ months after resection of a prepyloric gastric ulcer with anterior gastrojejunostomy and for 2 weeks had profuse watery diarrhea. Ulcer pain persisted and would be relieved by milk or antacids. Two and one-half months later gastroscopy revealed converging, puckering, inflamed folds of mucosa and, though crater was not seen, the general appearance was described as that of jejunal ulcer. Several roentgenograms revealed a barium-filled efferent loop but did not visualize the afferent loop. Symptoms, including vomiting and pain, recurred irregularly during 15 months at which time this emotionally unstable patient described tarry stools and streaks of blood in the vomitus. Because of this and general debilitation, two blood transfusions were given. Distress and regurgitation continued from time to time and 7 months later another episode of tarry stools lasting 2 days was described. However, on readmission after 3 weeks, roentgenograms revealed efferent and afferent loops normally filled with barium and gastroscopy revealed no evidence of ulcer. The stomach secreted no free acid even during an insulin test.

Another patient, following resection with antecolic gastrojejunostomy for prepyloric gastric ulcer and, within a few hours, re-exploration of the gastrojejunostomy because of exsanguinating hemorrhage, returned 1½ months later complaining of epigastric pain radiating to the back and of vomiting. Roentgenograms revealed a narrow stoma and an irregular rounded collection of barium or niche suggesting ulcer of the first portion of the afferent loop. Two standard histamine tests produced no free acid. Further x-ray examinations during the next 20 months revealed opening of the afferent loop but persistence of some obstruction of the efferent loop. The patient continued with weakness and episodes of vomiting, but there was no hematemesis, melena, or recurrence of pain.

Another patient, following resection and posterior Polya anastomosis for a duodenal ulcer which was left in place distal to the inverted stump of the duodenum, was relieved of symptoms except for gas and some spitting up of food. Three and one-half years later, however, he returned because of constant pain across the mid-abdomen present 5 weeks and relieved somewhat by taking milk. Roentgenograms revealed an area of spasm just below the stoma suggestive of marginal ulcer. Gastric secretions were not studied. He reported 15 months later that he must continue to diet and take medicine for the stomach and for diabetes.

Another, following resection with antecolic anastomosis for gastric ulcer, developed epigastric pain within a month; it occurred one or two hours after meals, awakening him at night. There was also some vomiting, which partly relieved the pain. He took a bland and then a milk and cracker diet during 6 months preceding return for examination. Roentgenograms, however, did not demonstrate ulcer and there was no free acid with a standard histamine test. Gastroscopy was also negative and emotional disturbances were pronounced. He was treated during two and one-half weeks in the hospital for a marginal ulcer. Symptoms continued 5 months later.

Recurrence following resection was treated by vagotomy in the remaining 3 of the 7 patients. Two months following subtotal gastric resection and repair of a gastrocolic fistula by excision of a segment of colon and end-to-end anastomosis, lateral repair of the defect in the jejunum, and antecolic gastrojejunostomy, one patient developed recurrence of tarry stools. Two weeks later hematemesis occurred twice following which there were frequently episodes of abdominal pain. Four months after the resection and repair he was hospitalized. Gastric secretion before and after histamine contained no free acid. Both gastroscopy and roentgenologic studies failed to reveal stoma ulcer. The red count had dropped to 2,300,000 and the hemoglobin to 6.8 Gm. It was thought by consultants that an acute ulcer had developed and perhaps healed. After transfusions exploratory laparotomy was performed. Some thickening was palpated at the anastomosis site and in the wall of the efferent loop. This was interpreted as being a healed stoma ulcer. Subdiaphragmatic vagotomy was carried out. Recovery was uneventful but the patient has not returned since discharge and cannot be traced.

Another patient, following resection for duodenal ulcer and antecolic gastrojejunostomy, got along well for 4 years except for a 20 pound weight loss. He then experienced 2 episodes of bleeding which were treated medically and without transfusions. Five years after operation he again developed tarry stools and then hematemesis and received 7 blood transfusions. Eight months later hematemesis recurred. One month later he was readmitted. Gastroscopy revealed no evidence of stoma ulcer. Roentgenologic examination did not reveal defect. Gastric secretions were not studied. Subdiaphragmatic vagotomy was performed. During exploration there was no evidence of scarring or of induration about the stoma, jejunum, or duodenal stump. Twenty-one days later he experienced colicky lower abdominal pain, some retention of gastric content, and was given Urecholine.

One month after resection with exclusion of a portion of the pylorus, and a posterior Pólya gastrojejunostomy for a duodenal ulcer with a duodenal hepatic duct fistula following an earlier operation, the third patient developed severe epigastric pain which was first relieved by taking food and then became more persistent, awakening her at night and making her require morphine. She was readmitted two months after the resection with these symptoms becoming more severe. Gastroscopic examination was unsatisfactory but no ulceration was noted. Roentgenographic studies revealed a poorly functioning stoma and probably an ulcer. Medical management was instituted, but after 2 months pain was worse and roentgenograms revealed 50 per cent 6 hour retention of barium with 2 large ulcer craters in the jejunum, 1 on either side of the stoma. A transthoracic vagotomy was performed by the surgeon who performed the first operation. Roentgenograms 3 months later revealed an open anastomosis with no evidence of ulcer. Three and one-half months after the transthoracic vagotomy abdominal pain recurred. During the next year she gained 25 pounds but was still bothered by epigastric pain which was relieved by milk and antacids, but gradually became worse. Fast-

ing gastric secretions were large in volume and had high values for free acid. Also insulin tests showed great increase of free acid both 3 months after vagotomy and at one year. Laparotomy was then performed by one of us (K. G.). An ulcer with a large crater was palpated in the jejunum. Also, a large mass of inflammatory tissue surrounded this area and extended to involve the stoma and the transverse colon. The esophagus was exposed and several large branches of the vagus nerve were found, removed, and later identified by microscopic examination. The small stump of excluded gastric antrum was also removed. Complete relief of pain followed, gastric secretions contained no free acid, and roentgenograms revealed healing.

Percentages of the resection patients having probable recurrence, 5.3 per cent, and operations for recurrence, 2.3 per cent, are illustrated in Table I. Also illustrated there is a 9.2 per cent group which consisted of 12 patients who reported by questionnaire symptoms suggesting possible but probably minor recurrence of ulcer. Symptoms were ulcerlike pain in 4, occasional tarry stool in 6, and 1 or 2 episodes of vomiting of blood in 2.

In Table I operative mortality and deaths during 5 years from all related causes following resection are compared with those among 135 patients in whom vagotomy was employed. The single operative death, 0.7 per cent, among the vagotomies occurred following transthoracic vagotomy and at the same time transabdominal pyloroplasty, a double procedure tried in 5 patients and then abandoned. The additional patient bringing deaths from all related causes following vagotomy to 1.5 per cent was caused 2 years after vagotomy for a stoma ulcer by continuation of a pre-existing gastrointestinal disturbance with diarrhea, nausea, and vomiting.

In Table I are also presented, for comparison, complication and recurrence percentages for the 81 patients who had vagotomy with gastroenterostomy, this number including all vagotomies associated primarily or secondarily with drainage procedures or performed for stoma ulcer following previous gastroenterostomy. Though no operations for recurrence were as yet necessary in this group, 1 patient is listed as having a probable persistence or recurrence, 1.2 per cent. A large stoma ulcer several centimeters down the efferent loop was visualized several times and produced symptoms of pain lasting a few weeks on 3 occasions and bleeding once during 19 months that have elapsed since vagotomy. The staff surgeon who did the operation and the consulting gastroenterologist agree that this vagotomy may be incomplete because of a positive insulin test. However, further operation does not yet seem justified. Of the patients with vagotomy and gastroenterostomy, 2.5 per cent report symptoms suggesting possible but minor recurrence of ulcer. These are ulcerlike pain and some anemia in 1 and pain in another lasting a few days and with 1 or 2 tarry stools on two occasions.

Similarly listed in Table I are the recurrences following vagotomy alone, a procedure abandoned 3 years ago. Recurrence of ulcer was proved in 4 patients, or 7.1 per cent. Of these, recurrence was in the duodenum in 3, 2 of whom were successfully treated by gastroenterostomy and 1 by resection. The fourth had persistence of a gastric ulcer following vagotomy. This was

treated by resection. Possible recurrence of ulcer is listed in 12.5 per cent, or 7 patients. It was evidenced in 5 with duodenal ulcer and 1 with gastric ulcer by occasional ulcerlike distress, particularly after dietary indiscretion. The seventh patient with a duodenal ulcer has described an occasional tarry stool. Fifteen patients, or 29.4 per cent, required secondary gastroenterostomy and are listed under secondary operations not for ulcer. Fourteen were for retention and 1 was performed at the time of reduction of an intussusception in the jejunum.

Not included in Table I are results of vagotomy performed for stoma ulcer following resection in 12 patients or resection and vagotomy performed together in another 3, once for persistent gastric ulcer, another time for persistent duodenal ulcer, and a third time at 1 operation for a patient with duodenal ulcer. One of the stoma ulcer patients has had pain and melena from time to time though there is no anemia and no evidence of ulcer. Another also with pain and melena had recurring episodes of intussusception of the upper jejunum requiring reduction once and treated a second time by resection of the involved area.

We have identified, among patients not previously described, 4 unfortunate individuals following resection, 7 following vagotomy with gastroenterostomy, and 4 following vagotomy alone who, though they have no evidence of ulcer, are emotionally unstable and appear and behave as though they are extensively disabled by various gastrointestinal and other complaints, some of which they attribute to their surgery. These patients are unable to fit properly into their social environment.

RESULTS OBTAINED BY QUESTIONNAIRE

Questionnaires were sent to the 123 resection patients currently believed living. Addresses were traced and correspondence again undertaken with those not initially replying. Exhaustive efforts aided by social service and other agencies have resulted in tracing and receiving replies from 113. Lists of the missing 10 patients were submitted to Departments of Vital Statistics of this and neighboring states but no deaths were located.

Of the 113 questionnaires received, 2 were on the 2 patients originally treated by vagotomy alone and then subsequently by resection. Since these 2 patients had vagotomy, their questionnaires are included in the vagotomy series and omitted here, leaving a total of 111. The average age of the resection series at the time of questionnaire was 50.1 years. Of these, 21 were over 60.

Identical questionnaires were sent at the same time to the 133 patients living after vagotomy. Eighty-one had had vagotomy and gastroenterostomy. Of these, vagotomy and gastroenterostomy were performed as 1 operation in 52 patients and vagotomy was performed a few weeks after gastroenterostomy in 2. Vagotomy alone was performed for stoma ulcer following previous gastroenterostomy in 12. The remaining 15 patients in this group of 81 had gastroenterostomies performed after vagotomy alone because of obstructive symptoms.

Thirty-seven of the 133 patients sent questionnaires are those of the original 56 who had vagotomy alone and have not as yet required secondary gastroenterostomy. Twelve of the group of 135 had vagotomy performed for stoma ulcer following resection. Two had it done preceding resection, 1 for a persisting gastric ulcer and the other for recurrence of a duodenal ulcer following vagotomy alone. A fifteenth patient with both vagotomy and resection had these performed at the same time for duodenal ulcer. Of the 135 patients 45 had a low economic or ward status.

Of the 135 patients sent questionnaires, replies were returned by 121. The average present age of the patients located was 45.4 years and their average age at time of operation was 42.7 years.

Change of Weight.—Each patient was asked his present weight, his normal weight during previous years, and his greatest weight. Also, patients reported whether they were gaining, losing, or maintaining their present weight. Reports are summarized in Table II, listing separately resections for duodenal ulcer and for gastric ulcer, and also results of vagotomy and gastroenterostomy, vagotomy alone, and particularly vagotomy and resection. It is evident that the average present weight of the 102 patients treated by subtotal gastric resection and reporting by questionnaire is 141 pounds as compared with 152 pounds for patients with vagotomy and gastroenterostomy, 154 pounds for 35 patients who still have vagotomy without gastroenterostomy, and only 139 pounds where vagotomy and resection have been added. The present average resection patient's weight of 141 pounds is 12 pounds below the average of weights which each patient had listed as his normal weight, and 29 pounds below their reported greatest weight preceding or during the early course of their ulcer. It seems particularly significant that, although 7 patients following resection gained an average of 16 pounds over their "normal" weight and 46 patients are currently within 10 pounds above or

TABLE II. AVERAGES OF WEIGHT OF PATIENTS IN POUNDS

OPERATION	AVERAGE WEIGHT IN POUNDS			CHANGE OF WEIGHT, NUMBER OF PATIENTS, AND CHANGE IN POUNDS					
				WEIGHT SAME ± 10 POUNDS		GAIN 10 POUNDS		LOSS 10 POUNDS	
	PRESENT	NORMAL	GREATEST	PT.	LB.	PT.	LB.	PT.	LB.
Resection for duodenal ulcer (68 patients)	145	155	175	30	–.6	5	16	33	23
Resection for gastric ulcer (34 patients)	138	150	162	16	–2	2	16	16	26
Total average of 102 questionnaires	141	153	170	46	–2	7	16	49	24
Vagotomy with gastroenterostomy (71 patients)	152	156	170	41	–1.8	5	21	25	19
Vagotomy alone for duodenal ulcer (35 patients)	154	153	168	21	–1.4	9	16	5	19
Total average of 106 questionnaires	151	155	169	62	–1.6	14	17	30	19
Vagotomy and resection (15 patients)	139	151	169	7	–3.1	1	15	4	30

below their "normal" weight, there remain 49 who are an average of 24 pounds below their "normal" weight, the extremes of loss being 50, 59, and 73 pounds in 3 patients. The average weight of 141 pounds is definitely below the expected or optimum weight at the age of 50. Also, as enumerated in Table II, average weights are somewhat higher in the group with vagotomy and gastroenterostomy or vagotomy alone and the number of patients losing weight is lower. Lowest average weight and greatest number of patients losing weight occurred in the group with vagotomy and resection. Twenty of the 111 patients with resection state that they are now gaining weight, 8 that they are losing weight, and 83 that they are maintaining weight without change. Of the 71 with vagotomy-gastroenterostomy 12 report that they are gaining, 9 losing, and 50 maintaining weight.

Ability to Work.—Patients were asked whether they were able to work full time, half time, or less. Replies are tabulated in Table III, A as percentages. Sixty-five of the 111 patients treated by resection were able to work full time, 34 half time, and 12 less than half time or not at all. Grouping of reports according to type of ulcer preceding resection revealed that 48.5 per cent of the gastric ulcer patients worked full time, 37.2 per cent half time, and 14.3 per cent less. Of the duodenal ulcer patients, 63.3 per cent worked full time, 26.4 per cent half time, and 10.3 per cent less. Of 21 resection patients over the age of 60 years 8 report working full time, 9 half time, and 4 less. Three stated that they had retired and another patient at 54 stated that he had to retire because of weakness. Causes of disability in the total group of 111 resection patients were weakness or easy fatiguability in 27, abdominal or ulcerlike pain in 7, retirement in 4, anemia in 4, nervousness in 2, and "dumping" syndrome in 2. It is of interest that 77 of the resection patients or 71.3 per cent state that they are able to work better than before their operation and only 31 or 28.7 per cent state that they are able to work less than before resection.

TABLE III. RESULTS OF RESECTION, VAGOTOMY WITH OR WITHOUT GASTROENTEROSTOMY, AND VAGOTOMY AND RESECTION

	RESECTION (111 PATIENTS) (PER CENT)	VAGOTOMY AND GASTRO-ENTEROSTOMY* (71 PATIENTS) (PER CENT)	VAGOTOMY ALONE (35 PATIENTS) (PER CENT)	VAGOTOMY AND RESECTION (15 PATIENTS) (PER CENT)
A. Ability to work				
Full time	58.5	77.5	77.4	53.3
Half time	30.7	15.5	17.0	20.0
Less	10.8	7.0	5.6	26.7
B. Able to work better than before operation				
Yes	71.3	81.8	91.2	66.6
No	28.7	18.2	8.8	33.4
C. Satisfaction of patient				
Complete	76.6	71.9	64.4	53.3
Moderate	16.2	21.1	32.4	40.0
Dissatisfied	7.2	7.0	2.9	6.7

*Includes all vagotomies with primary or secondary drainage or done for stoma ulcer following previous gastroenterostomy.

It is evident (Table III, A and B) that ability of patients to work is somewhat greater or more frequent following vagotomy and gastroenterostomy or vagotomy alone and is definitely less where vagotomy and resection have both been performed. Causes of disability after vagotomy and gastroenterostomy in 71 patients were weakness in 9, nausea 1, retirement 1, nervousness 2, and diarrhea in 3.

Over-all Satisfaction of the Patient.—Patients were asked whether they were completely or well satisfied, moderately satisfied, or dissatisfied with result of operation. Replies are given in percentages on Table III, C and compared with replies from the 3 vagotomy groups. Fifty-two of the 68 patients treated by resection for duodenal ulcer listed complete satisfaction, 13 moderate satisfaction, and 3 dissatisfaction. Twenty-four of the 34 patients resected for gastric ulcer described complete satisfaction, 5 moderate satisfaction, and 5 dissatisfaction. The patients resected for gastrocolic fistula (2), marginal ulcer (3), or both duodenal and gastric ulcer (4), were each well satisfied. Patients were also asked their opinion of the operation. Of 107 replying, 72.9 per cent said good, 19.6 per cent fair, and 7.5 per cent poor or bad. In the over-all vagotomy group of 116 patients, 75.0 per cent said good, 18.9 per cent fair, and 6.1 per cent poor or bad.

Gastrointestinal Functions.—Questions were asked concerning appetite, bowel movements, and abdominal discomfort or gas pain. In the resection group appetite was reported as good by 61 per cent, fair by 29 per cent, and poor by 10 per cent. In the vagotomy-gastroenterostomy group reports were respectively 58 per cent, 38 per cent, and 4 per cent. In the group with vagotomy alone reports were 60 per cent, 31 per cent, and 9 per cent. Hunger after missing a meal was described as experienced by 72 of 106 resection patients reporting. Thirty-one of 68 vagotomy-gastroenterostomy patients reporting and 14 of 35 of the series with vagotomy alone described hunger. Nausea was described as occurring occasionally by 25 of the resection group and by 24 of the over-all vagotomy group. Vomiting was described by 13 of the resection group and by 18 of the combined vagotomy group as occurring at times.

The usual number of bowel movements in the resection group was described as 1 or 2 each day, only 3 patients describing 3 bowel movements on some days. The usual number reported by vagotomy patients was also 1 or 2 bowel movements per day, 16, however, describing 3 on some days and 5 describing 4 or 5 and 6 or 8 at times. Occasional episodes of diarrhea were experienced by 9 of the resection patients and by 45 of the vagotomy patients. Constipation was reported by 12 of the resection group and 8 of the vagotomy group as occurring either regularly or occasionally. In general, bowel movements were normal or hard in the resection group more frequently than in the vagotomy group, and soft or watery more frequently in the vagotomy group.

Patients were asked if they experienced weakness, pallor, cold sweat, or abdominal pain during the first hour after eating. These symptoms were described as occurring at times by 12 patients of the resection group and 17

of the vagotomy group. Sensations of improper or delayed emptying of the stomach were reported by 5 of the resection group and 22 of the vagotomy group. Abdominal pain usually resembling gas pain was experienced at times by 16 of the resection group and 30 of the vagotomy group. In response to another question asking specifically whether they experience gas on the intestines, cramps, bloating, rumbling, or colic, 30 of the resection group and 54 of the vagotomy group described these.

In response to the questions, "Can you eat any foods you want?" and "Do you now need any medicine?" 29 of the resection group reported limitation of diet either to taking of small amounts at one time or avoidance of fried or rich foods, and 4 reported taking antacids, 3 vitamins, 7 iron or liver. Of the vagotomy series, 22 described some limitation of diet and 33 reported taking medicines, usually Urecholine, Sorlate, Banthine, or some other treatment prescribed by us for symptoms.

Each patient was asked whether he had noted one or more tarry stools or hematemesis and whether he considered himself anemic. One or more tarry stools were described by 7 of the resection and 6 of the vagotomy patients. Hematemesis was described by 3 resection patients and 1 vagotomy as occurring once or more. In response to questions concerning red blood count, hemoglobin, or anemia, 27 of the resection patients and 11 of the vagotomy patients described anemia and many evidenced this by low counts or taking medicine for anemia.

Patients were asked whether they were now as strong as before operation and in reply 43.9 per cent of the resection patients stated that they were weaker than before operation as were 32.2 per cent of the vagotomy patients. Patients were also asked how they considered their nerves and requested to check any of fourteen adjectives which applied to their condition. The adjectives were lazy, indifferent, alert, energetic, anxious, conscientious, apprehensive, high-strung, carefree, worried, content, irritable, restless, and happy. In direct answer to the question and as confirmed by the adjectives checked 48.2 per cent of the resection patients stated that their nerves were good, 23.2 per cent fair, and 28.6 per cent bad. Answers of the vagotomy group were 38.1 per cent good, 37.2 per cent fair, and 24.7 per cent bad.

DISCUSSION

It must be emphasized that good results have followed subtotal gastric resection, vagotomy with gastroenterostomy, vagotomy alone, and even combination of vagotomy with resection. Poor results or complications have been emphasized in this report in order to evaluate these operations. Because of poor results surgery is and has been employed only for patients with serious ulcer problems. We believe that any treatment directed toward ulcer alone could not be expected to relieve all symptoms or effect social readjustment in some of these patients. The several series reported are made up of patients who with few exceptions had serious disability and whose habits with food and drink were at times intemperate.

The series of different operations studied to compare poor results and complications were unfortunately not entirely similar, partially because the incidence of gastric ulcer which occurs more frequently in older individuals was higher in the resection series, 39 in 132, and lower in the vagotomy series, 7 in 135. The age of resection patients averaged 5 years older. The average age of the resection group at the time of their operation was 48 years and of the vagotomy group 43. Average age at the time of questionnaire was 50 years in the resection group and 45 in the vagotomy group. Surgery for stoma ulcer following resection or gastroenterostomy was, however, more frequent in the vagotomy series. Also, the percentage of private patients was lower in the resection group, being 32.6 per cent, and higher, 67.4 per cent, in the vagotomy group. The average time since operation in the resection group was 28.3 months and in the vagotomy-gastroenterostomy series 26.4 months. Although exact comparison of these series of operations is not possible, we believe that results of the record study abstracted in Table I indicate significantly greater mortality risk, rate of deaths from all causes associated with surgery, incidence of nonfatal surgical complications, and incidence of postoperative ulcer with resection than with vagotomy. It appears that vagotomy with gastroenterostomy is a safer procedure for duodenal or stoma ulcer than subtotal gastric resection.

Since most of the difficulty following resection was related to handling of indurated or extensively scarred duodenal ulcers, it would seem that regardless of preference surgeons might consider or employ vagotomy-gastroenterostomy rather than resection when these circumstances are found during exploration. Exclusion procedures employed in 28 of the resections were associated with complications requiring secondary operation in 9. There were no deaths in this group. Although nonfatal complications were lower when the ulcer was removed or the duodenum closed proximal to the duodenal ulcer, all deaths in the resection series attributable to surgery occurred following these techniques and from associated inadvertent injury to the common duct, the portal vein, or the pancreas.

Less significant but strongly suggestive is the evidence obtained by questionnaire showing advantages of vagotomy with regard to weight of patients (Table II), ability to work, and rehabilitation (Table III, A and B). It is interesting to note, however, that the percentage of patients describing complete satisfaction (Table III, C) was somewhat higher for resection and the percentage of those moderately satisfied was higher for vagotomy. This is probably explained by the higher incidence of minor disorders such as gas pains and change of bowel habit toward looseness following vagotomy. Percentages of patients dissatisfied were equal in the two groups. Poorest results were described by patients having both vagotomy and resection. Highest rate of rehabilitation occurred among those who as yet have had vagotomy alone. However, vagotomy without drainage was abandoned 3 years ago as a sole treatment for duodenal ulcer because of the high incidence of secondary operations and of recurrence of ulcer.

Though we are now reassured concerning merit of our preference for vagotomy with gastroenterostomy as the procedure of choice for patients with duodenal, stoma, and even juxta-esophageal gastric ulcers, we recognize that a final conclusion cannot be based upon a comparison of series of procedures for ulcer performed during a 5 year over-all period. Development of methods of treatment of complications such as steatorrhea, "dumping" syndrome, anemia, gas pains, and so on, which follow in varying incidence either resection or vagotomy will influence late results. Regardless of final outcome of studies or final general agreement among surgeons concerning merit of resection or vagotomy, it is definitely evident to us that patients following either procedure should be carefully observed and appropriately treated for complications which may develop.

CONCLUSIONS

1. Subtotal gastric resection was associated with a higher mortality rate, a higher incidence of surgical complications, and more frequent occurrence of postoperative ulcer than vagotomy with gastroenterostomy.

2. Although either resection or vagotomy with gastroenterostomy effects a high incidence of satisfactory results and rehabilitation, each has an associated occurrence of disappointing results.

3. Decision regarding preference of operation will depend upon results of longer periods of contemporary observation and of developments which may decrease the risk of resection and also aid the treatment of postoperative complications following either procedure.

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DISCUSSION

DR. R. BOWERS.—This is an excellent study and I just want to ask a question or two about something that is not clear. I presume that I missed the point.

Have you compared the results of your gastric resections with the gastroenterostomies or vagotomy plus gastroenterostomy group?

I wish to congratulate you on your good results with gastric resection and particularly your low incidence of duodenal stump blowouts, unless some of the reported subhepatic and subdiaphragmatic abscesses were due to this complication. This complication should never happen when a surgeon performs gastric resection for duodenal ulcer, because the possibility of successful duodenal stump closure must be decided before the resection is attempted. One cannot do a proper gastric resection, in my opinion, unless the duodenum can be mobilized, which aids greatly in safe closure of the duodenal stump.

Another important point implies that the duodenal ulcer must not be removed during the resection if, in doing so, satisfactory closure of the stump is jeopardized.

I believe your results favorably reflect these viewpoints and I commend you for it.

DR. J. FARRIS.—I wonder if I can ask Dr. Lyons whether he has any figures on the percentage of instances in which it was possible to remove the ulcer in the gastrectomy series.

I would also like to mention briefly the experience we have had in the Birmingham Veterans Hospital, Van Nuys, California, where I am associated. Dr. Weinberg and his colleagues have completed recently a follow-up study on 350 vagus resections. In most of these cases a supplementary drainage operation has been done—either gastroenterostomy or pyloroplasty. Many of these operations are likewise being done by trainees or men who are participating in the resident training program, and it is gratifying, in evaluating these figures, to find that there has been only one death in the 350 patients.

The results are being reported by Dr. Weinberg elsewhere, but it is safe for me to say that good results have been obtained in 90 per cent of this group. Thank you.

DR. E. HOWES.—I would like to ask if you would integrate your figures of deaths from gastric resections with mortalities reported from other clinics. I feel sure that if our mortality from gastric resection was as large as is reported here—and I would say that we do a fair number a week—the Saturday before last, for example, there were five on the schedule on one morning—that we would soon abandon gastric resection and do vagotomies with gastroenterostomy.

It is my impression that our mortality is not nearly as high as the figure here*; and the figure you gave also does not approximate what the Mayo Clinic reports for gastric resections.

Also, I noticed that you did not analyze the number of complications reported around the country from doing vagotomy.

I think it is only fair to integrate those figures as they come from other clinics, along with data from your clinic.

DR. K. S. GRIMSON (Closing).—In response to Dr. Bowers' question we feel that there is little objection to comparison of results of resection with gastrojejunostomy and of vagotomy with gastrojejunostomy since either operation includes a gastroenterostomy. Several years ago our results indicated that vagotomy without gastroenterostomy should not be employed. In this series of resections about one-third of the duodenal ulcers were left in place distal to the closure of the duodenum, one-third were removed, and about one-third were treated by an antral exclusion.

*Actual mortality: no deaths from elective gastrectomy for peptic ulcers (approximately 300 cases) during the years 1947, 1948, and 1949.

In answer to Dr. Howes' question concerning mortality rate of resection it has been difficult to obtain accurate contemporary reports from surgeons or hospitals. I believe mortality rates range from about 1 per cent where operations are usually performed for selected groups of private patients to around 4 per cent in our clinic where we are receiving patients in poor condition and with seriously complicated ulcer and up to around 10 per cent in certain hospitals through the country. By and large, resections have been accomplished with a higher mortality risk than vagotomy-gastroenterostomy.

Dr. Postlethwait, though he did not speak, has collected over-all mortality statistics on vagotomy throughout the country and found the average less than 1 per cent.

Dr. Howes also asked about the over-all picture and our incidence of complications as compared with that of others. There may be some difference between the patient material we worked with and that of other clinics. Dietary and intemperate habits and poor environment of some of our patients may explain in part the high incidence of postoperative difficulty. In general our results of vagotomy and gastroenterostomy are better than our results of resection, though results of either operation may be a little inferior to reports of some others.

AIDS IN THE MANAGEMENT OF ILEOSTOMIES; A NEW PLASTIC BAG

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BALTIMORE, MD., AND BYRON D. SMITH, M.S.,‡ MINNEAPOLIS, MINN.

AT THE University of Minnesota Hospitals and the Minneapolis General Hospital, the employment of ileostomy in the treatment of certain cases of idiopathic ulcerative colitis and of colic polyposis has become a rather routine matter, relatively free of the once-feared pain and risk of widespread skin erosion, breakdown of wounds, and prolapse of bowel. This has become possible through the employment of the Koenig-Rutzen bag§ and the adoption of a single-barrel ileostomy technique devised specifically for such a bag.[1] The technique has been altered somewhat, but remains specialized for a prosthesis which is cemented firmly to the skin precisely to the mucocutaneous junction.[2]

Despite our satisfaction with the operative method and the Koenig-Rutzen bag, certain problems have arisen. Any irregularity of the skin leads to an increased likelihood of seepage of the highly irritating ileac secretion between the bag surface and the skin. As Rutzen has recommended,[4] any appliance which holds the bag with considerable sustained pressure for a few hours against the abdomen has been found to lead ordinarily to prompt healing of such erosions. In instances refractory to this measure, the use of a split mattress and prone position a day or two[1] has regularly solved the problem.

Prevention of erosion is far easier than healing after erosion has occurred. The early postoperative management has been much simplified with this in mind. At the time of surgery, the bowel is left closed by interrupted silk sutures. At forty-eight hours, when intestinal activity is ordinarily just beginning to return, a No. 16 French catheter with multiple holes is slipped into the bowel through the center of the suture line and secured with a pure-string suture of 000 catgut on an atraumatic needle. Placement of a second such purse-string suture 3 to 4 mm. wide of the first suture five days after surgery regularly prevents leakage, and the arrangement permits satisfactory Wangensteen suction emptying of the ileum until a full week after operation, when a Koenig-Rutzen bag can be directly applied.

A second problem, and one which is most distressing to Mr. Rutzen, appears to be related to the use of rubber in the bag. About 10 per cent of the cases under the care of the group at Minnesota appear to produce in the intestinal tract a material which causes rapid deterioration of the rubber. Bags become irregularly blackened, thinned in areas, much increased in dimensions, and very friable. In two patients, new Koenig-Rutzen bags sprang large leaks after less

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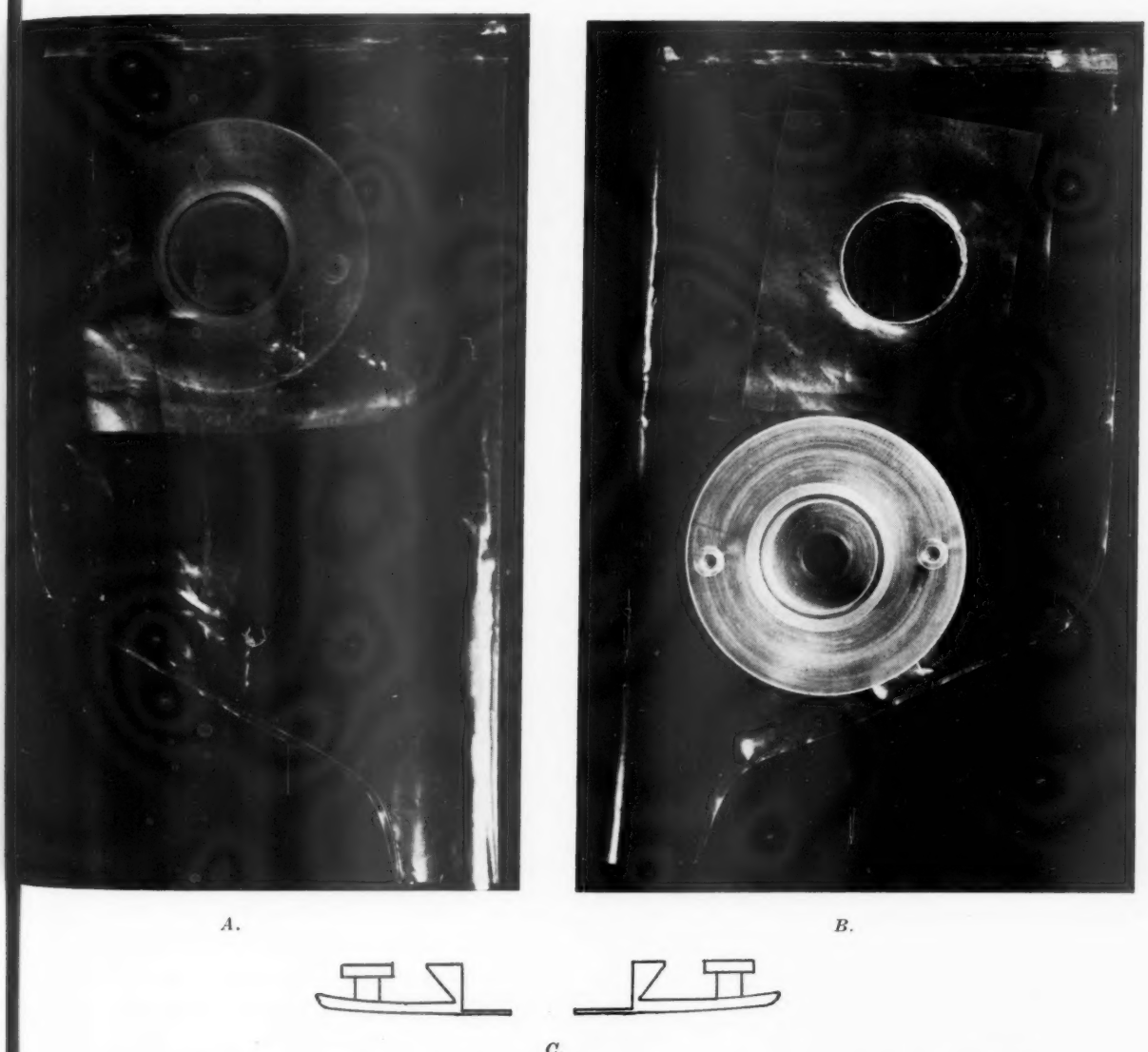
§Obtained from Mr. H. W. Rutzen, 3952 North Lowell, Chicago 41, Ill.

than ten days of use. The reactions of this relatively small group of patients has led to a search for a type of bag which would be resistant to ileac drainage from any individual.

In looking for suitable materials and designs to care for the few patients who cannot use the Koenig-Rutzen bag, the following criteria must be met: (1) skin reactions must not occur; (2) firm sealing to the skin must be possible; (3) materials must be resistant to all ileac discharge; and (4) the apparatus must be comfortable to wear, convenient to empty, inconspicuous under clothing, and esthetically acceptable.



A. *B.*

C.

Fig. 1.—Methyl methacrylate and polyethylene ileostomy bag: *A*, front view; *B*, rear view with face plate removed for detail; *C*, cross-section of plate. Two extra thicknesses of polyethylene are sealed to the bag at the orifice for application of tension as an aid in slipping bag over flange of face plate. Size and shape of orifice of face plate may be adjusted at bedside by a hand machinist's reamer. Drain at bottom may be closed by rubber band, as in the Koenig-Rutzen bag. Face plate is sealed to the skin by Dermatome cement on the plate and Rutzen skin cement on the skin. (Diameter of face plate, 9 cm.)

Lucite had already been found to produce little tissue or skin reaction,[3] and Lucite face plates for application to the skin have been in use for nearly three years at University of Minnesota Hospitals. Over a period of many months, Vinylite bags* have been attached to these plates, but have been discarded because the material becomes discolored and stiff within a few days. Early in 1949 the decision was made to use polyethylene bags attached to a deeply grooved flange on the face plate by over-wrapping with rubber binders. This combination has performed well to date, although the tensile strength is less than desired.

The detail of the present bag is indicated in the accompanying illustration. Opaque white bags are being obtained, as less offensive from an esthetic point of view than transparent containers.

Rutzen cement does not adhere well to the Lucite face plate. Ordinary Dermatome† cement is spread on the face plate, and Rutzen skin cement on the skin. After drying for three minutes, the bag is applied precisely, and adhesion is as secure as is the case with the standard Koenig-Rutzen bag.

A third problem has arisen in the apparent sensitivity of the skin of a few patients to the rubber cement. A method for use of a special pressure sensitive adhesive tape‡ has been under study in collaboration with the Minnesota Mining and Manufacturing Company, which may eventually overcome this problem as well.

At the present time, twelve patients have worn such appliances as have been described and have contributed ideas and criticisms which have brought the apparatus to the present state. Steps are planned to make such an apparatus generally available in the near future.§

SUMMARY

1. Methods to assure sound healing and healthy skin about ileostomies are indicated.

2. A bag is described which is valuable in those ileostomy patients whose discharge destroys the rubber of the Koenig-Rutzen bag.

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*Manufactured as hot water bottles by the Alden Wonder Plastics Company, Minneapolis, Minn.

†Obtained from V. Mueller & Company, Chicago, Ill. Manufactured by Padgett-Hood Assemblage Company, Kansas City, Mo.

‡Through the courtesy of L. W. Lehr and Bert Auger, "Scotch" Tape Division, Minnesota Mining and Manufacturing Company, St. Paul, Minn.

§A Lucite and Polythene bag of very different design is marketed by Saul Saetz of Burlington, Vt. It came to our attention some months after adoption of our present design. The bag does not satisfy the criteria outlined in this paper in that it is bulky and insecure. After exchange of information, he also is evaluating a Minnesota Mining and Manufacturing Company type of cement.

A NEW SURGICAL TREATMENT FOR HIRSCHSPRUNG'S DISEASE

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(From The Children's Hospital, Children's Medical Center, and the Department of Surgery, Harvard Medical School)

THE pathology in Hirschsprung's disease is generally considered to be limited to the dilated portion of the colon. Recently, evidence has accumulated raising questions in connection with this theory and supporting the concept of a functional obstruction in the rectosigmoid which produces secondarily the hypertrophied and dilated colon. This evidence is as follows:

1. Colostomy relieves all of the symptoms of Hirschsprung's disease and in three to six months the dilated colon becomes normal in size and much of the hypertrophy disappears.[1] If the primary pathology were in the dilated colon, no relief should be gained from a colostomy. One would expect relief from a colostomy if the basic pathology were a low partial colonic obstruction (Fig. 1). Closure of the colostomy in patients with Hirschsprung's disease produces a recurrence of the disease in three to four months.

2. Barium enema studies on patients with Hirschsprung's disease provide additional evidence of pathology in the rectosigmoid.[2] Careful examination of the colon demonstrates that the distal dilated sigmoid has a funnel-shaped outline and that the rectosigmoid is narrow and irregular (Fig. 2). Frequently, this lesion is difficult to outline either by fluoroscopy or by roentgen films. It can best be demonstrated by the injection of a small amount of barium, with the patient in the oblique position. Most important, the dilated sigmoid must be manipulated out of the pelvis to permit a clear view of the rectosigmoid.

3. The motility of the colon in Hirschsprung's disease has been studied and it has been found that the dilated colon has normal, integrated peristalsis. Furthermore, it has been demonstrated that patients with Hirschsprung's disease have no peristalsis in the rectosigmoid, in contrast to normal individuals. It is postulated that this absence of peristalsis results in a partial functional obstruction.[3]

4. The resection of this functionally deficient segment of colon by a special technique in fifty-two patients has relieved their symptoms.

5. Histologic study of the specimens of colon surgically removed from patients has demonstrated the absence of Auerbach's plexus in the rectosigmoid.[3] Similar findings have been reported from other studies.[4-8] According to Cannon, peristalsis cannot take place in bowel in which Auerbach's plexuses have been destroyed.[9]

It would seem on the basis of this evidence that the fundamental lesion in Hirschsprung's disease is a congenital one, consisting of a failure of development of Auerbach's plexuses in the rectum and rectosigmoid. Auerbach's plexuses contain the ganglia of the parasympathetic supply to the bowel. Most of the

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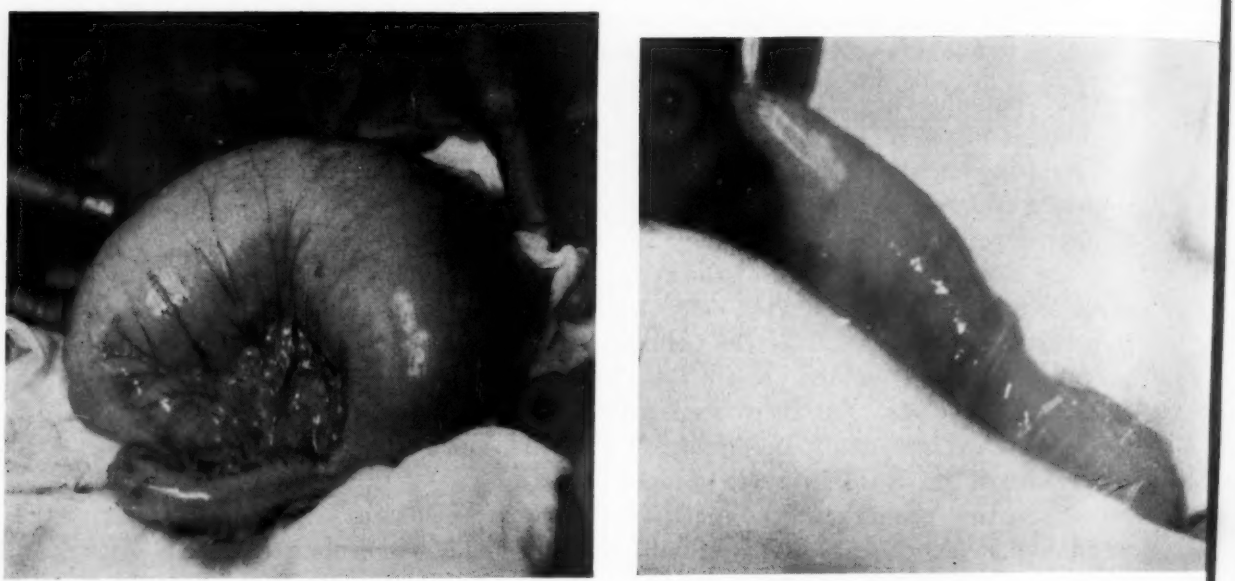
colon, including the descending portion, probably receives its parasympathetic supply from the vagus. The distal end of the colon receives its parasympathetic supply from the pelvic nerves. Failure of the pelvic parasympathetic supply to develop may be the explanation of the location of the lesion in Hirschsprung's



A. *B.*

Fig. 1.—*A*, Photograph of sigmoid during course of colostomy. *B*, Photograph of same bowel four months later at time of resection.

Fig. 2.—Barium enema showing narrowing in rectosigmoid and dilatation of the sigmoid.

disease. The dilated colon in Hirschsprung's disease contains normal nerve structure. This evidence indicates that therapeutic efforts should be directed to the rectosigmoid and rectum and not to the dilated colon.

The selection of patients with megacolon suitable for surgical therapy depends on the demonstration of a narrowing of the rectosigmoid by barium enema studies. Patients with a colon dilated down to the anus do not have Hirschsprung's disease, according to our concept, and will not benefit from resection of the rectosigmoid and rectum.

Out of the first twenty-two patients with Hirschsprung's disease treated surgically, sixteen had a colostomy performed as a preliminary measure. As our experience has grown, fewer colostomies have been performed. All colostomies are now performed in the transverse colon and are of the simple loop type.

In only six of the last thirty patients has a colostomy been considered necessary. In five of these cases the infants were extremely ill and primary resection was considered inadvisable. In one patient it was impossible to prepare the bowel for a primary resection.

Preoperative preparation, which begins four weeks before admission to the hospital, consists of a low residue diet, two ounces of mineral oil daily, and one to two enemas each day. When the patient is admitted for operation, a large rectal tube is inserted for a sufficient distance to permit the end to be in the dilated colon. It is taped in place and colonic washings are then performed three times a day. Usually the tube can be positioned quite readily. However, in one patient proctoscopy under general anesthesia was performed to position the tube. Even this procedure failed in a second patient and this accounts for one recent colostomy. After the rectal tube has been in place twenty-four to forty-eight hours the patient's abdomen is scaphoid and he is ready for primary resection.

Most patients with Hirschsprung's disease have a defective urinary bladder. Of twenty patients in our group studied by cystometrogram preoperatively all except one had hypotonic bladders. The bladder capacity of these patients before any detrusor contractions occurred was considered far above average. This is probably further evidence of a defective pelvic parasympathetic supply. The presence of a defective bladder is extremely important from a technical standpoint for slight damage to the bladder innervation during operation may result in urinary retention.

The experimental work on which our special technique for resection of the rectosigmoid and rectum is based has been described previously.[1] The patient is placed in a lithotomy position which permits access to both the abdomen and the perineum (Fig. 3). The draping is so arranged that at the completion of the first stage of the operation the removal of a heavy double sheet from the legs of the patient exposes the perineum without disturbing the abdominal drapes.

A suprapubic incision slightly to the left of the midline is used. The sigmoid loop is delivered and usually the transition from dilated to narrow

colon occurs at the junction of the sigmoid and rectosigmoid. However, in our series, varying portions of the sigmoid have been involved and in three patients all of it was narrow. In two patients, all of the colon from the left one-half of the transverse to the anus was involved. In three patients only the rectum was involved.

Pathologic studies have demonstrated the absence of Auerbach's plexus to extend some distance into the dilated bowel. Therefore, the proximal point of resection should be at least 12 cm. proximal to the point of narrowing to insure removal of all of the lesion.

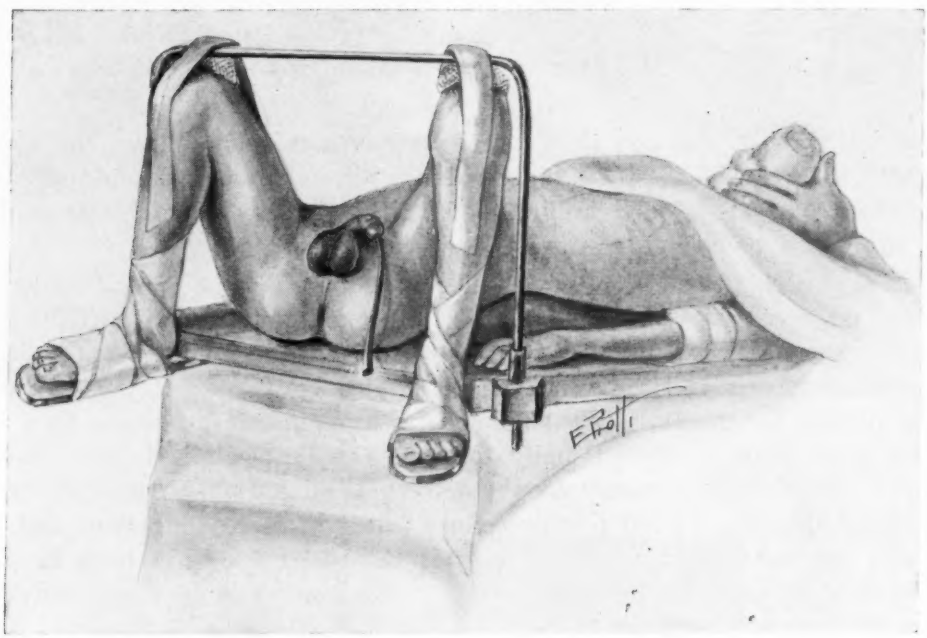


Fig. 3.—Position of patient on operating table.

The next step is to free the colon proximal to the resection so that it can be brought to the perineum. There is always adequate bowel; the limiting factors are the blood vessels. To free the sigmoid sufficiently it is necessary to divide the sigmoidal branches at their origin (Fig. 4). An arcade system is thus preserved which supplies the circulation of the bowel adequately. On six occasions we have taken down the splenic flexure and divided the left colic artery, thus permitting resection of most of the descending colon and sigmoid. In two patients a left hemicolectomy was performed with division of the middle colic artery. So far there has been no failure of the blood supply to the bowel proximal to the resection.

The dissection of the rectosigmoid and rectum is then performed right down to the internal sphincter. This must be done with great care or there may be permanent damage to the innervation of the bladder. It must be remembered that patients with Hirschsprung's disease have a damaged bladder mechanism. Therefore, the margin of safety is small in these patients and the dissection must be performed carefully.

It is our practice to remove a segment of bowel to facilitate pulling the distal part through the anus. Using the von Petz clamp the bowel is divided at the previously selected point of resection and again distal to this at the juncture of the sigmoid and rectosigmoid (Fig. 4). The remaining stump of sigmoid can readily be pulled through the anus.

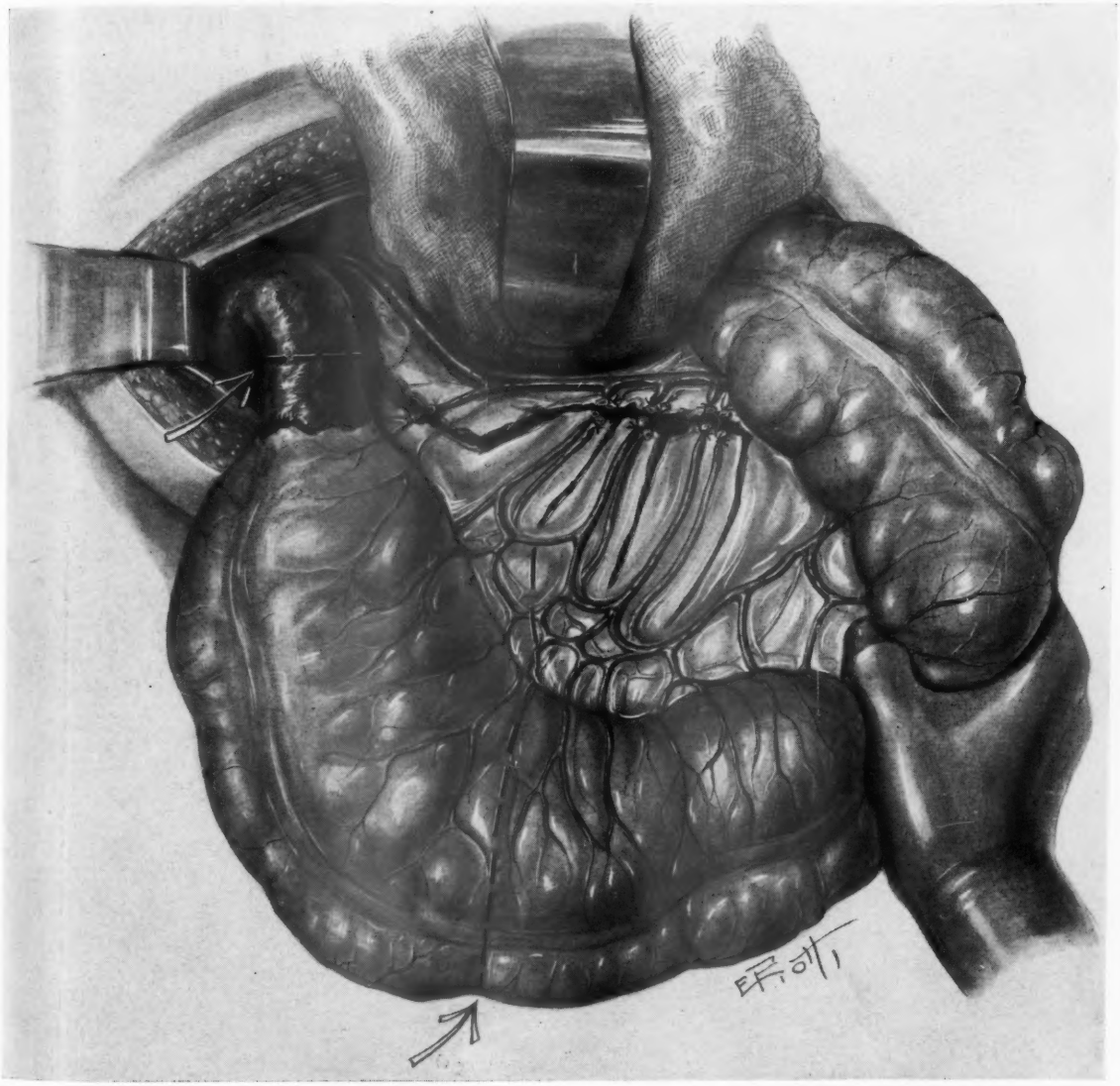


Fig. 4.—Drawing showing the division of three sigmoidal branches. The broken lines indicate the segment of bowel which is resected. This facilitates pulling the rectosigmoid out through the anus.

At this stage of the procedure the operative team is divided into two groups and the drape over the legs is removed, exposing the perineum. The sphincter is dilated and a long clamp inserted through the anus up to the closed end of the rectosigmoid (Fig. 5). The end is grasped and pulled down through the anus, turning the bowel inside out. This segment, protruding from the

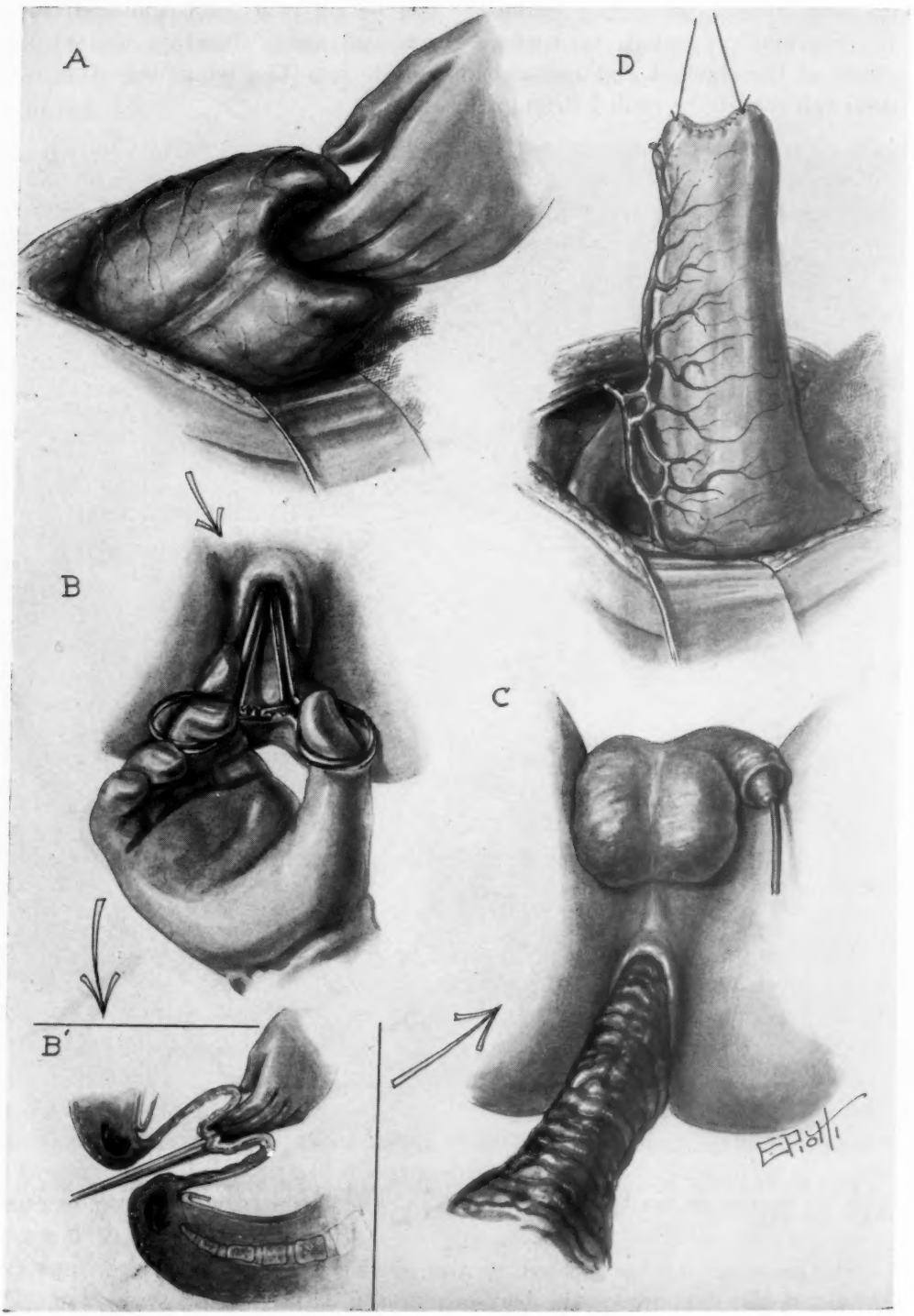


Fig. 5.—*A* and *B*, A clamp is inserted through the anus and the closed end of the rectosigmoid is grasped. *B*[1], The bowel is then pulled out through the anus. *C*, The segment now protrudes with the mucosa on the outside. *D*, The proximal bowel has two sutures placed to facilitate pulling this segment through.

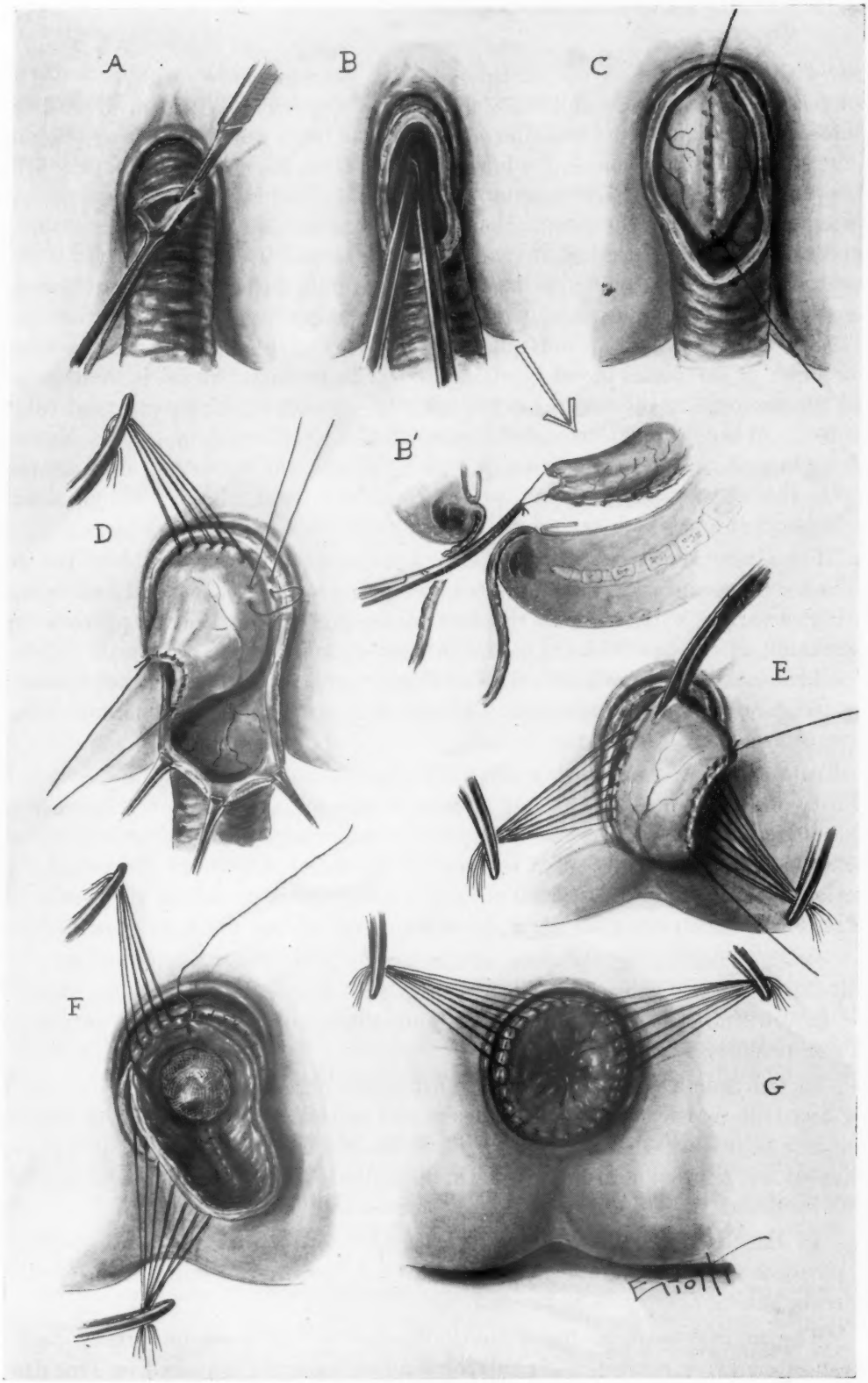


Fig. 6.—*A*, After the bowel is prepared and drapes placed, a cut is made 2 or 3 cm. from the mucocutaneous margin. *B*, A clamp is inserted through this orifice and the sutures on the proximal segment grasped and the bowel pulled through as in *C*. *D*, Interrupted silk sutures are used to approximate the muscular coats. *E*, The proximal bowel is opened. *F*, The mucosae are approximated with catgut sutures. *G*, Completion of the anastomosis. After all the sutures are cut, the anastomotic line will retract up through the anus.

anus with the mucosa on the outside, and the perineum are scrubbed with ten sponges soaked in 1:1000 aqueous Zephiran. The perineum is then draped and a table of instruments and supplies set up for the team working at the perineum. A cut is made halfway across the bowel 2½ cm. from the cutaneous margin (Fig. 6). A long clamp is then inserted through this opening into the pelvis, and the operator at the abdominal incision, having attached two sutures to the proximal bowel, places them so that they are grasped by the clamp. It is then possible to pull the proximal segment down through the pelvis and out through the distal segment. The anastomosis is made, using first a row of interrupted silk sutures to approximate the muscular coats. As these sutures are placed the remainder of the distal bowel is cut across. The proximal bowel is then opened and the mucosae of the two segments are approximated with interrupted catgut sutures. When the anastomosis is completed it is allowed to retract through the anus and assumes a position 2 to 3 cm. from the mucocutaneous margin. While the anastomosis is being made below, the team at the abdominal field reconstruct the pelvic floor and close the abdominal wound.

The alternative to this pull-through type of anastomosis would be the performance of an anterior resection—a procedure which has several disadvantages in Hirschsprung's disease. In the first place, in the pull-through operation we remove all of the bowel down to the internal sphincter. In the small pelvis of a child a low anastomosis would be difficult to perform and therefore some of the lesion would not be removed. Two recurrences following such procedures have come to my attention.

In the second place, using the pull-through technique we can perform resection on most patients without making a preliminary colostomy because the discrepancy in size of the two segments is minimized by the dilatation of the distal segment as the proximal segment is pulled through. If the anterior resection is contemplated, a preliminary colostomy is required to permit the dilated bowel to return to the approximate size of the distal narrow segment.

In the third place, stricture at the suture line is less likely to occur if a pull-through anastomosis is made. The dilated colon permits a large stoma at the suture line and we have had only one slight narrowing of the suture line in our primary resections.

In the fourth place, with the pull-through procedure the exposure during the anastomosis is excellent so that leaks and infection are rare. There has been one case of infection in our group. This was not a routine case, as it was complicated by a previous colostomy which limited the length of bowel available and hindered the establishment of a satisfactory anastomosis.

In the fifth place, our method reduces the operating time and permits us to perform resection on sick patients who would require a preliminary colostomy were an anterior resection to be used.

The management of the urinary bladder is the most important part of the postoperative regime. The inlying bladder catheter is placed on free drainage for four days. Tidal irrigation is then used until the tenth postoperative day, when the catheter is removed. We have had only two urinary complications.

The first was infection one week after discharge, which responded to penicillin. The second was difficulty in emptying the bladder. This symptom cleared up two weeks after the catheter was removed. Furmethide was used during this period and seemed to be of value.

Postoperatively, the patients are given a regular diet without laxatives or mineral oil. Occasionally, during the early postoperative period, before peristalsis is present in the colon, it may be necessary to insert a rectal tube two or three times a day to help decompress the patient.

Following discharge from the hospital, the patients have a diarrhea lasting sometimes from three to six weeks. Gradually they settle down to a system of one to two bowel movements a day.

One slight stricture has occurred in this series of thirty-one patients with primary resection and it was probably due to tension on the suture line. It was corrected by a short course of digital dilatations. There have been three other strictures, all in patients with preliminary colostomies. The colon had shrunk to 2 cm. or less in diameter and the stoma at the anastomosis was correspondingly small. Later, as the bowel dilated to normal size, the suture line remained fixed in size and required dilatation. This experience stresses the necessity of allowing only three to six weeks between colostomy and resection. If the interval is much longer, the bowel becomes so small that a narrowing at the suture line is inevitable. These patients have also done well on digital dilatation.

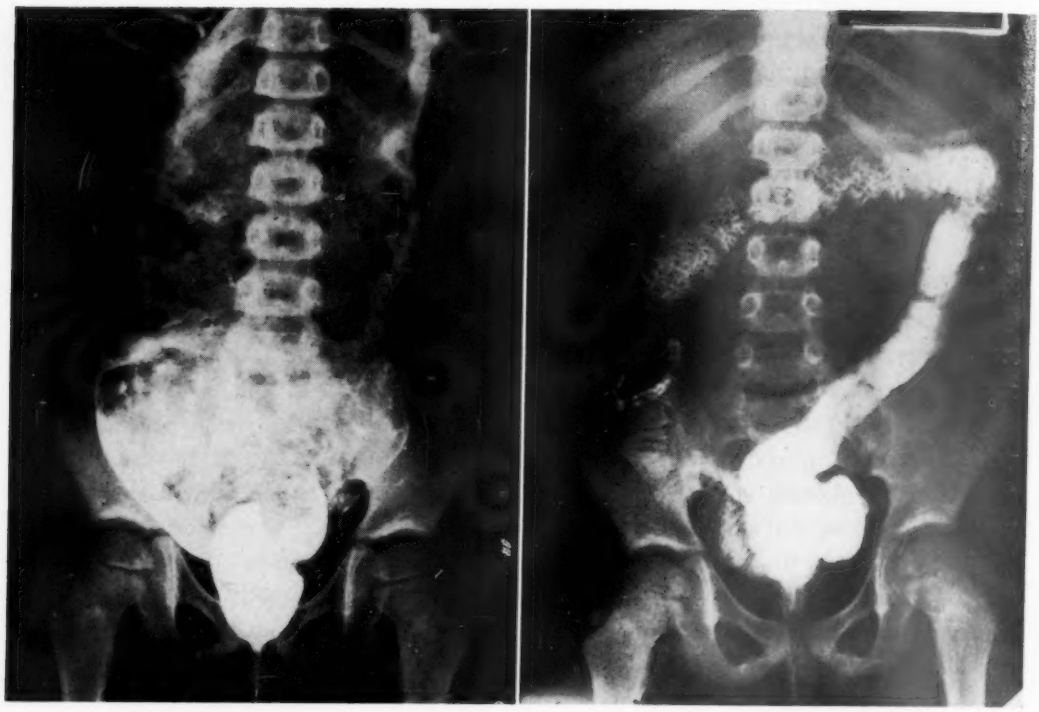
The most frequent complication has been acute gastroenteritis, which these patients tolerate poorly. This difficulty has occurred in nine patients, most of them under 2 years of age. Three children were seriously ill, with vomiting, distention, and diarrhea. We have found that the best treatment has been the insertion of a rectal tube and colonic washing. In two to three days the patients have recovered, the abdominal distention has disappeared, and bowel movements have become formed and regular.

We have had one failure in a group of fifty-two patients operated upon. This was a baby 2 weeks of age who did not have a typical lesion at operation. The sigmoid and rectosigmoid were resected and no ganglion cells were found in the resected bowel. Abdominal distention and constipation recurred two months after operation. By x-ray examination the lesion was found to extend to the splenic flexure. A second resection has recently been performed on this patient.

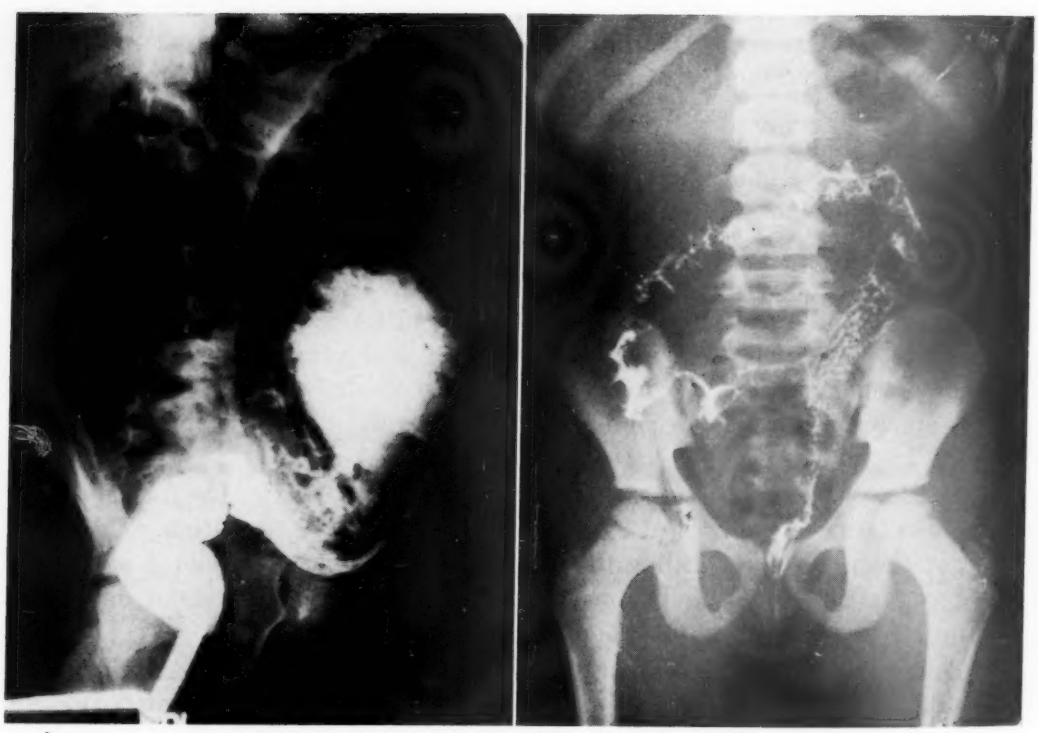
It is well to avoid operating on infants if possible. In the first place, in babies the lesion is not typical by x-ray examination or at operation. Dilatation has not taken place to outline the extent of the lesion. At 6 to 8 months of age the typical dilatation has occurred; consequently, there is no danger of failing to remove all of the lesion.

There has been one postoperative death which occurred in the case of a 3-week-old infant following a primary resection. Intestinal obstruction developed, which was corrected. However, eventually the baby died of agranulocytosis.

The remaining patients have been completely relieved of their complaints. The longest follow-up is almost three years. All of the patients have normal



A.



B.

Fig. 7.—*A*, Preoperative barium enema and a checkup three months after operation. *B*, Preoperative barium enema and a repeat six months after operation.

sphincter control. They are all on normal diets, with no mineral oil or other laxatives, and have one to two bowel movements a day. All of them have gained weight and are in good general health.

Our results with this form of treatment have been corroborated by Stephens.[8] After visiting us and observing our method he returned to England and subsequently operated upon twenty-eight patients using our technique. There were two postoperative deaths. In the remaining patients he reported good clinical results.

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DISCUSSION

DR. K. GRIMSON.—Dr. Swenson certainly deserves a good word for his excellent studies and congratulations on his large series. He has well demonstrated that like colostomy, the pull-through procedure will effect reduction in the size of the colon. His concept of the etiology is probably correct, but during seven years of study of approximately thirty megacolon patients we have not been able to prove it.

The normal-sized but abnormally functioning lower sigmoid and rectum, according to our balloons and other observations, is not functionless but rather, though working abnormally, can contract and particularly dilate.

Four years ago, we reported our belief that surgery was generally unnecessary for the sigmoid-achalasia type of Hirschsprung's disease or megacolon. In spite of Dr. Swenson's operations and reports our additional experiences have strengthened this belief. Many of our patients had dilatation of the descending and sigmoid colon as great as those presented by slides this afternoon. However, with an improved medical program of treatment these children were carefully carried through a few troublesome years following which symptoms usually subsided and bowel movements occurred regularly in later life.

Only in three patients who did not have the sigmoid-achalasia type of megacolon but rather had enormous enlargement of the right, transverse, and upper left colon above a normal-appearing rectum and lower sigmoid was primary operation considered necessary and performed. In these, as reported, we used a colectomy and ileosigmoidostomy to direct the liquid content of the terminal ileum into a segment of the distal and not dilated sigmoid. The stump of sigmoid left should be short.

In only one additional patient during the study period in this series was surgery necessary. For this child a pull-through procedure was done because of previous surgery starting with a colostomy shortly after birth. The result has been only moderately satisfactory, some dilatation and some obstipation persisting.

I certainly feel that Dr. Swenson has given a very nice demonstration and that his studies and experiences should aid us in determining cause and proper treatment of megacolon.

DR. M. RAVITCH.—This is a large, beautiful series and the results could hardly be improved upon. But there still remain some facts to be explained about Hirschsprung's disease and its histopathology.

When Bodian and Stephens revived the idea of the absence of the ganglion cells in the segment which Dr. Swenson had felt was the site of the disease, they began operating—Stephens did, after Dr. Swenson—and have now a considerable series. It is their opinion that uniformly, the ganglion cells are absent in the narrow distal segment, and at times this absence extends several centimeters into the dilated section.

I have studied their sections in a considerable number of cases and must say the findings they describe in the sections they have can be seen by anyone.

In a very small number of cases of our own, we have not been able to convince ourselves with certainty that the absence of ganglion cells in the narrow segment is invariable, and is not perhaps some type of artifact due to technique or varying thickness of the bowel or contraction or twisting.

I would like to ask Dr. Swenson whether he still feels as he stated in a recent publication that those histologic abnormalities in his experience are not invariable.

The other thing which is difficult for us to explain is the fact that we have had clinically quite good results from resection of the left colon, much as Dr. Bell reported some years ago, beginning to the left of the middle colic artery and going down well into the pelvis. If there is a narrow segment, we go down into it; if there is not a narrow segment, we do a conveniently low, safe, aseptic, closed anastomosis.

Several months ago we operated upon a girl of 14 who had never had a spontaneous stool. She had the most elegant narrow segment imaginable going up almost to the splenic flexure. Knowing that Dr. Stephens and Dr. Swenson would have resected the narrow segment and left the dilated segment, we resected the dilated and left the narrow, anastomosing the ileum to the descending colon. She began having spontaneous stools the second or third day and has had them ever since, although she had never had them before. She has not had an enema for the three or four months since the operation.

I wonder if it is possible that some of the results achieved from this ingenious operation are due to straightening out the redundant bowel. The two patients, for instance, in whom a rectal tube could not be passed might very well have had a chronic volvulus. In several cases we have seen the bowel twisted on itself as it lay across the junction of the narrow and dilated bowel.

We have tried this pull-through procedure. It is technically easy and perfectly satisfactory as an operation, but thus far, in a much smaller series than Dr. Swenson's, we prefer the results with resection of the left colon.

DR. G. HUMPHREYS.—I want to join in stating that I think the concept of Hirschsprung's disease as being due to physiologic disturbance in the small segment is a tremendous contribution in treating this disease. Dr. Hiatt at Presbyterian Hospital started to work on this about four years ago and has paralleled the work of the Boston group very completely.

In our balloon studies, the function has been similar to what Dr. Grimson just described, that is, rather than finding a functionless segment we find one that does contract but contracts in a mass rather than in a peristaltic way.

In other words, if one puts three balloons in the distal small segment rather than having two in the dilated and one in the small, one finds that the wave which comes down to that segment then causes a mass contraction which in effect causes an obstruction.

Now the histology has puzzled all of us, also. I think some of the discussion is confused by a statement that Auerbach's plexus is absent. That segment is not devoid of nerves. There are plenty of nerves in it as far as we can see histologically. It is apparently

lacking in ganglion cells and that seems to be the source of the confusion, since there is no good basis for judging what the normal number of ganglion cells is.

It is our conception that this physiologic imbalance may vary a good deal in different patients. Some may have a very sharply limited area and others may have a line of demarcation which is much less distinct, so that they have a more or less funnel-shaped end to their dilated colon; and that where this area of deficient but not completely absent innervation comes down to the rectum, one has the group in whom the dilated bowel extends right to the rectum or may actually overcome the rectal sphincter tone, and so apparently result in the spontaneous remission later in life that Dr. Grimson speaks of.

It certainly has been a great help in treating these patients to have this concept. Dr. Hiatt's operation is a pull-through operation very much like Dr. Swenson's, and we have had equally good results—again in a much smaller series.

DR. C. E. KOOP.—I shall make my remarks very brief. About three years ago we gathered together sixteen patients who had megacolon and I was about to publish a paper stating that chronic volvulus was the etiological factor. At that time I knew of Dr. Swenson's work and set about reviewing our own cases, and have proved to my own satisfaction that he is correct. Our balloon studies have paralleled his. Our clinical impressions have paralleled his, and histologically we see the changes in the myenteric plexus in about 80 per cent of patients.

I think the pertinent thing about my comment is that in those sixteen patients we did anterior resections as low as we possibly could. They all did well for fourteen months. After fourteen months three of them had recurrence of their symptoms with changes in the barium enema. Of those three patients I have operated again on two of them and have done the pull-through procedure.

In reviewing the previously excised bowels and the present excision of bowel, the changes in the myenteric plexus support Dr. Swenson's thesis.

Since that time we have carried out an additional fourteen pull-through procedures with no failures.

DR. O. SWENSON (Closing).—The pathology of Hirschsprung's disease has been carefully studied and there is a unanimity of opinion in the published reports. Dalla Valle, in 1920, was the first to report absence of Auerbach's plexus in the distal colon. Roberts and Kernohan reported the same findings in Hirschsprung's disease in 1938. Tiffin, Chandler and Faber, in the *American Journal of Diseases of Children* in 1940, and Zuelzer and Wilson, in the same journal in 1948, reported absence of Auerbach's plexus in congenital megacolon.

Cannon demonstrated experimentally that destruction of Auerbach's plexus resulted in absence of peristalsis. This agrees completely with our motility studies. In the segments of bowel where there was an absence of peristalsis by motility studies there were no Auerbach's plexuses in the microscopic sections.

In following patients with anterior resection or resection of the dilated colon alone, three or four months' follow-up is not sufficient. This disease is the result of a functional partial obstruction and therefore in some cases recurrence does not occur until six to eight months postoperatively.

We have followed up some of our patients almost three years now and they continue to be perfectly well.

THE PRINCIPLE OF COMPLETE EXCLUSION IN FISTULAS OF THE SMALL INTESTINE

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THE management of external fistulas of the small intestine is often a very difficult problem. Excluding the vital treatment of the rapid deterioration of the patient's general condition from fluid and electrolyte loss, there are technical aspects of the surgical approach which deserve emphasis. It is with the latter phase that this report is concerned, and with fistulas distal to the second portion of the duodenum. Proximal duodenal fistulas obviously do not lend themselves to exclusion. In fistulas of the rest of the small intestine the principle of complete exclusion is usually followed when dealing with active disease such as ileitis, or with tumors; but in traumatic, surgical, and simple obstructive fistulas too many attempts at local cure have been the rule, with subsequent breakdown and recurrence.

Hartzell,[1] in 1938, reviewed the various methods of controlling these fistulas by nonoperative, conservative means. He devised an ingenious rubber stopper to protect the skin and conserve the vital digestive juices while healing was allowed to occur spontaneously. However, at best, these local methods have been only partly successful, and postponement of prompt cure results in a steady downhill course. Surgical intervention then becomes very hazardous. With present-day knowledge of substitution and replacement therapy patients can be prepared for formal surgery rapidly, and added safety is achieved by the use of the antibiotics.

Although Trendelenburg[2] and von Hacker[3] in the last century described the exclusion principle, Keyes and Middleman[4] in 1941 stated that "The operation is generally unfamiliar." They reported three cases at that time and Dr. Keyes added several more in 1942[5] which illustrated various techniques, in each instance employing the exclusion principle. Probstein[6] has also emphasized the importance of the operation for early restitution of intestinal continuity following exteriorization of small intestinal segments. The excellent operation of Dennis and Varco[7] for the management of strangulated femoral hernia makes use of the principle. Obviously there are many situations in which exclusion is performed automatically as the only logical procedure, but this report is primarily concerned with stressing its importance in simple persistent fistulas in the absence of organic disease.

Because of previous contact with Dr. Keyes, I performed exclusion of traumatic fistulas during the war from the beginning. In many cases the abdominal wall was greatly damaged, and the fistula was very difficult to handle due to its association with a huge denuded area. All injured tissue was considered out-of-bounds for surgical attack; incision was planned through normal tissues only, even if this incision were a considerable distance away from the

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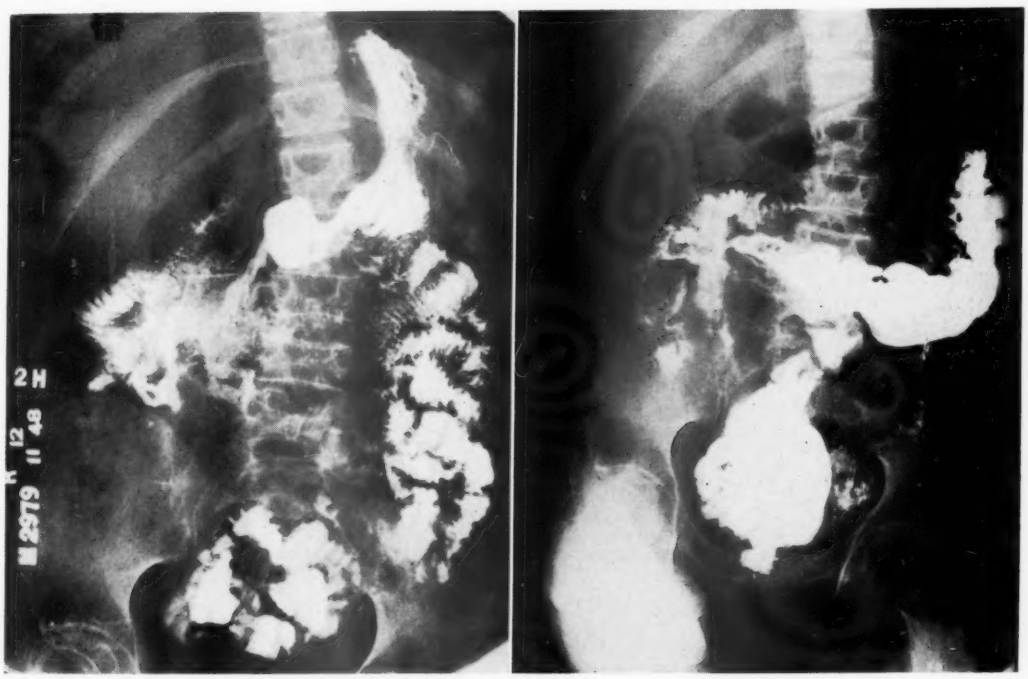
fistula. A semblance of normal peritoneal cavity was usually encountered. Identification of the proximal and distal limbs of the fistula could be greatly simplified in certain cases by the preoperative insertion of a Miller-Abbott tube which was allowed to come out through the fistula; thus any bowel containing tube was known to be proximal, and bowel without tube was distal. Transection of both limbs through normal tissue and careful anastomosis re-established an intact intestine immediately. The excluded limbs were turned in and left in situ, unless complete resection could be done at the time. This was seldom feasible because of the serious condition of the patient. There were no failures or leaks in these war casualties where normal tissues could be used.



A. *B.*

Fig. 1 (Case 1).—*A*, X-ray picture of barium by mouth, showing a fistula in the upper jejunum. *B*, X-ray picture of barium by rectum, showing fistula also at ileocolic anastomosis.

Recent experiences in civilian practice presented similar problems, the trauma usually being surgical. It is to be noted especially that in the following cases despite poor condition and scarring from multiple operations, exclusion in stages was carried out with technical ease and with minimal disturbance to the patient. The essential points in the technique are easily stated. The general condition of the patient is meticulously evaluated in terms of depletion and indicated restorative therapy carried out. The location of the fistula is determined by X-ray pictures of barium given by mouth, by rectum, and through the fistula itself. Gross location is easily settled by timing the appearance of dyes after oral administration. Patency of the entire bowel distal to the fistula must of course be proved, since obstruction is often the cause of persistence, as in Case 2. Intestinal intubation may be valuable in certain cases. Operation is

performed according to the technique described for the war cases. Two fundamental principles stand out: first, to stay away from the fistulous areas entirely, and second, to operate only through normal tissues, both in the abdominal wall and in the peritoneal cavity. The area of the fistula is contaminated, edematous, and scarred; the secretion is chemically irritating; and usually the topography of the involved area is very complicated and frustrates attempts at careful anatomic dissection.

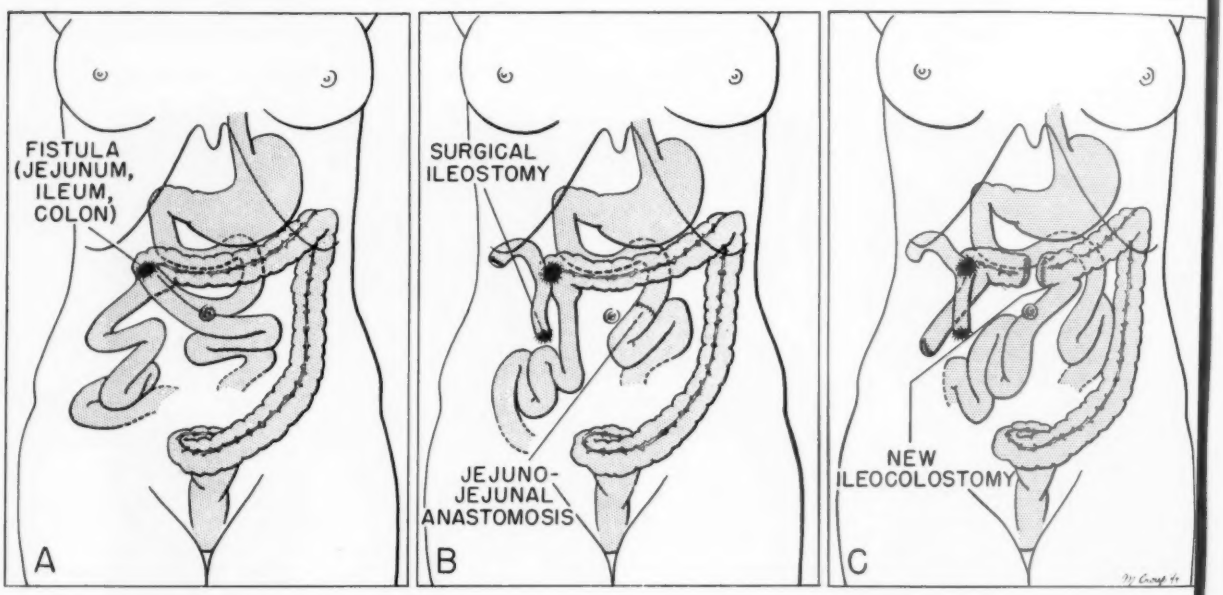


Fig. 2 (Case 1).—*A*, Diagrammatic sketch of situation preoperatively (a resection of the right colon had been done previously). *B*, the first stage procedures: exclusion of the jejunal component with end-to-end anastomosis and jejunostomy. *C*, the second stage procedure: exclusion of the ileocolic component with side-to-side ileocolostomy.

There are three choices for disposition of the excluded fistulous loop. It may be closed at both ends and left in situ, the fistula itself serving to decompress it. Or one end of the loop may be brought to the skin for decompression should it be feared that the isolated fistula might heal. Or finally, before abdominal closure, the limbs may be freed up to the peritoneal attachment of the fistula, to be resected locally after closure of the main abdominal incision. In the following illustrative cases staged procedures were necessary for reasons indicated in the histories.

CASE 1.—This 16-year-old girl was admitted to the Children's Hospital on Oct. 25, 1948. She was extremely cachectic, weighing but 38 pounds. The right hip was fixed in 90° flexion and both knees showed flexion contractures, which were solely the result of being in bed a long period of time. There was a small intestinal fistula in the center of a right rectus incision, the discharge from which had markedly excoriated the surrounding skin. Significant laboratory findings were a red blood count of 3 million and a total protein of 5.79 Gm.

Seventeen months previously, after progressive weight loss and right lower quadrant pain, she had been operated upon for appendicitis. Ileitis was found and a short time later the right colon and terminal ileum were resected, with ileocolostomy. The wound broke down, a fistula developed and persisted for the next seventeen months. The pathologic specimen

was said to have shown ileitis. During this period she had not been out of bed, and during the downhill course the family was told that she was "full of holes" and that "nothing could be done." Bowel movements by rectum had continued.

X-ray studies on admission showed no evidence of ileitis, but revealed that both the jejunum and the ileocolic area were involved in the fistula (Fig. 1, *A* and *B*, and Fig. 2, *A*). It required three weeks of intensive preparation before surgery could be undertaken. Whole blood, 1,500 c.c., was given. Multiple vitamins, protein digests, and skim milk were administered by mouth. At the time of operation the red blood count was 4.3 million, plasma proteins were normal, and the general condition was much improved. Exclusion of the jejunal component of the fistula was accomplished on November, 19 through a left rectus muscle-splitting incision (Fig. 2, *B*). One limb of the excluded segment of the jejunum was brought out below the fistula for safety. Her condition did not warrant the second exclusion at this time. The contracture of the right hip complicated the ease of laparotomy quite

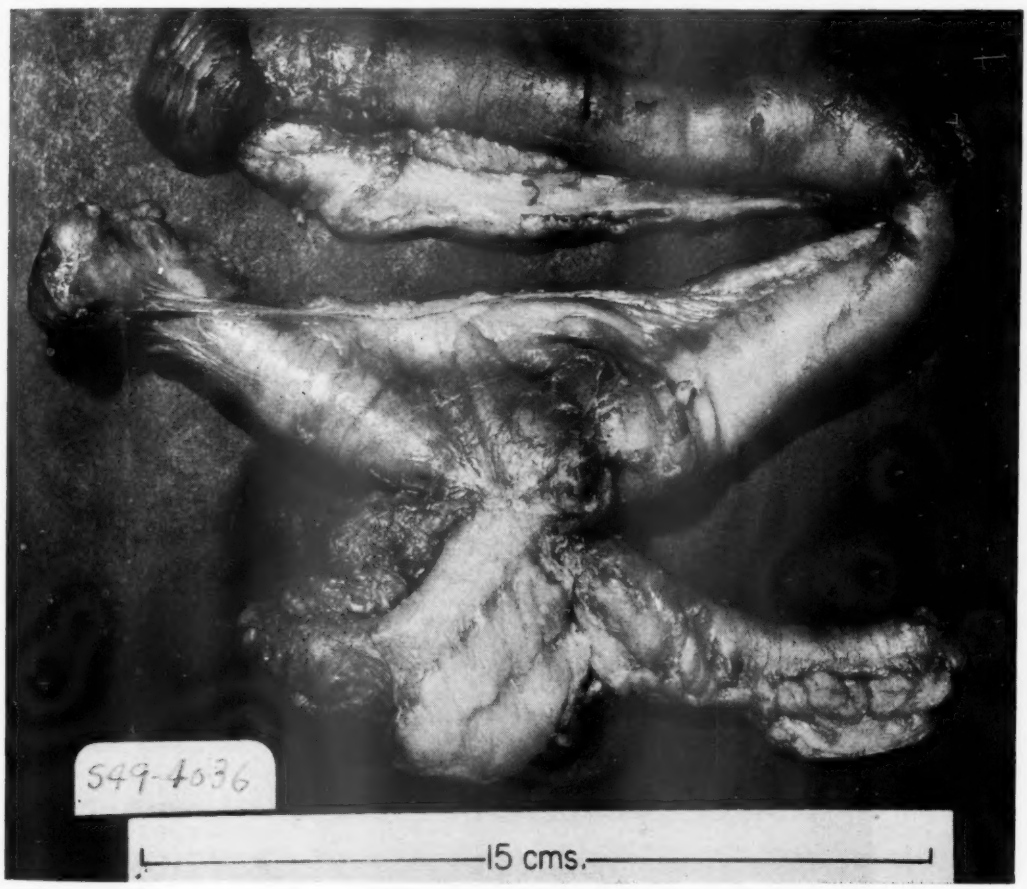


Fig. 3 (Case 1).—Photograph of the resected excluded segment showing jejunal limbs superiorly and ileocolic segment inferiorly.

uniquely. Convalescence was remarkably smooth and the incision healed *per primam*. She was transferred to the convalescent unit, the contractures being treated by traction. Ileal contents continued to be discharged from the fistula, but, of course, with less irritation to the skin. The exclusion of the ileocolic component was performed on Jan. 27, 1949, through the same left rectus incision (Fig. 2, *C*), thereby establishing complete restitution of the intestinal tract, leaving the excluded segments entirely sidetracked, and the fistula purely mucus in type. (The original fistula then closed, the surgical jejunostomy permitting de-

B.

A.

Fig. 4 (Case 2).—*A*, Barium enema showing the sigmoid-cecal fistula, the obstruction in the transverse colon, and the multiple diverticuli in the nonfunctioning left colon. *B*, A clearer view of the sigmoid-cecal region. *C*, Injection of barium into the fistula, demonstrating fistula between ascending colon and ileum. (Residual barium in left colon from enema.)

compression.) The general improvement was then rapid and constant. While having continuing treatment for the contractures she finished high school, and returned for resection of the excluded bowel in November, 1949. At this time she had more than doubled her original weight (90 pounds) and signs of normal puberty had developed. She was walking with the help of a brace on the right leg. Resection of the nonfunctioning bowel and repair of the abdominal wall defect were accomplished on November 29 at the Woman's Hospital. Again there was a smooth convalescence. The resected specimen (Fig. 3) showed no evidence of ileitis, nor had biopsies obtained at the two previous operations.

Fig. 4, *C*. (*For legend see preceding page.*)

CASE 2.—In December, 1947, a 51-year-old woman presented herself with a colostomy in the right upper quadrant, and a history that for the two previous months, following an operation, no stool had passed by rectum. Examination showed that small intestinal content was being discharged through the colostomy. The opening was in the center of a wide scarred area and the skin excoriation was intense. She was somewhat obese and in a very good state of general nutrition.

Her previous surgical history was long and involved. Her troubles began nine years previously in May of 1937, when gall bladder drainage had been performed for a serious, acute illness. There was bile drainage for six months. In June, 1940, she had a repair of an incisional hernia. Repeated gall bladder attacks occurred for several years, culminating in a rupture of the gall bladder and generalized peritonitis in March, 1946. Following operation for this she developed a persistent fecal fistula. In June, 1946, a local attempt at closure of the fistula resulted in infection and recurrence of the fistula. A year later, the fistula still being present, she was operated upon for intestinal obstruction, her fifth laparotomy. Finally in October, 1947, another local attack was made upon the fistula. Postopera-

tively she became markedly distended, the wound broke down and the fistula recurred; she noted that the discharge was much more irritating to the skin. Bowel movements by rectum ceased.

X-ray studies on admission to the Woman's Hospital showed that the fistula was in the ascending colon but there was also an ileocolic fistula, obstruction in the proximal transverse colon, and a large sigmoid-cecal fistula (Fig. 4, *A*, *B*, and *C*, and Fig. 5, *A*). The left colon was of very small caliber and showed multiple diverticuli.

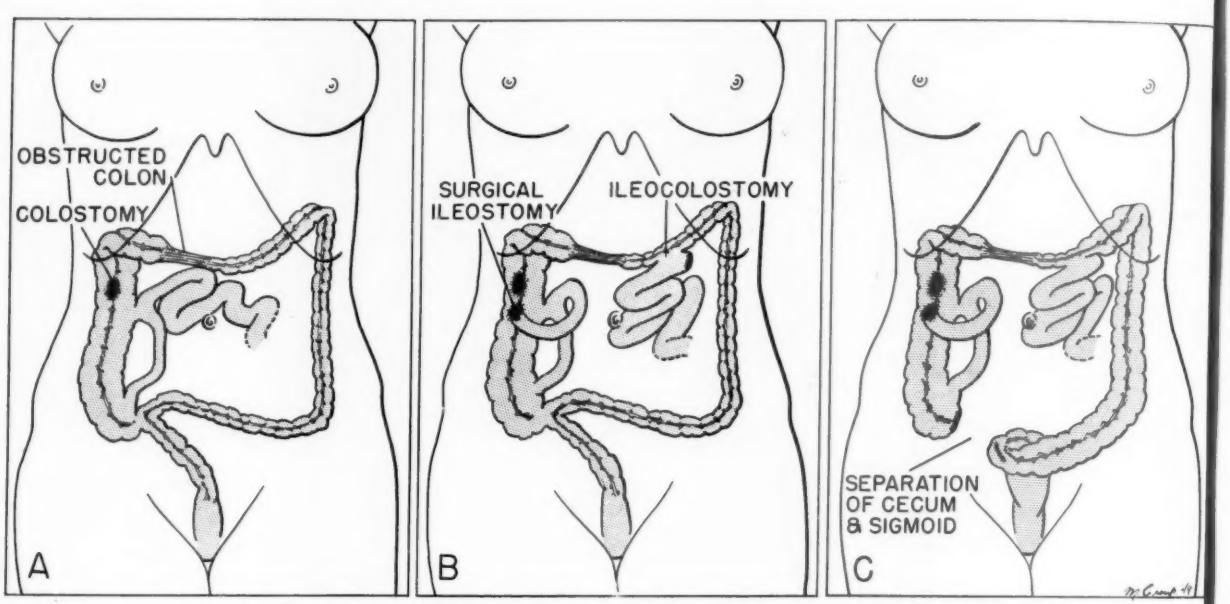


Fig. 5 (Case 2).—*A*, Diagrammatic sketch of the situation preoperatively. *B*, The first stage operation; sidetracking ileocolostomy, surgical ileostomy. *C*, The second stage operation: separation of cecum and sigmoid colon.

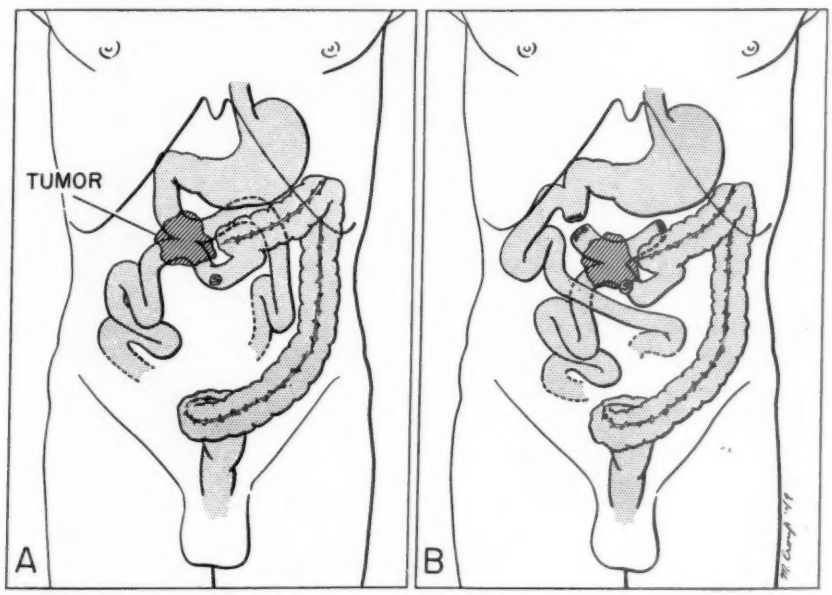


Fig. 6 (Case 3).—*A*, Diagrammatic sketch of the situation preoperatively (the right colon had been resected previously for carcinoma). *B*, The duodenojejunal exclusion.

Operation was performed on Jan. 5, 1948, through a lower transverse incision, well away from the fistula and all the scarred tissue in the right upper quadrant. Great difficulty was experienced with adhesions, but the ileum proximal to the internal ileocolic fistula was finally identified, transected, and the proximal end anastomosed to the small but normal distal transverse colon. The distal ileum was brought outside the abdominal wall for safety. The sigmoid-cecal fistula was identified, and appeared to have been purposely created, but was not disturbed at this time (Fig. 5, *B*). Postoperatively, although rectal bowel movements were re-established, there was considerable reflux from sigmoid to cecum and out through the external fistula. The discharge was not irritating and the patient postponed the second operation until November, 1948. At this time the sigmoid was detached from the cecum, leaving a completely sidetracked mucus fistula and an intact intestinal tract (Fig. 5, *C*). The patient has been so content with the result that she has not desired resection of the mucus fistula (leading to the right colon and terminal ileum). But she has continued to have attacks of cholecystitis, and it is anticipated that the badly mangled upper right quadrant will some day have to be explored.

A third case is added for the purpose of illustration, but concerns an internal fistula due to carcinoma.

CASE 3.—This patient was a 56-year-old man who developed a duodenoileal fistula nine months after a resection of the right colon for carcinoma of the hepatic colon. The severe diarrhea and rapid downhill course warranted exploration even though hopeless recurrence was felt to be the cause. Operation in August, 1949, demonstrated a large tumor mass involving duodenum, ileum, and the main mesenteric vessels (Fig. 6, *A*). Palliation was obtained by the exclusion principle, the jejunum being anastomosed end-to-side to the proximal duodenum at the level of the ampulla of Vater. The duodenal and jejunal limbs attached to the tumor were turned in, the fistula being trusted to decompress the loop (Fig. 6, *B*). Palliation was effected for three months, but the patient has now succumbed. Autopsy showed no recurrence of the fistula.

SUMMARY AND CONCLUSIONS

The value of the exclusion principle in the cure of small intestinal fistulas is re-emphasized. Local attempts at closure are seldom justified. Operation must be done through normal tissues according to the techniques described. Patients who are given up as hopeless may be cured by relatively simple and safe surgery.

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DISCUSSION

DR. BOWERS.—I think Dr. Harbison's cases show us what can be done if we vigorously persist in employing sound surgical principles in taking care of these people. I

had much more experience with these dreaded fistulas at Walter Reed Hospital, where these cases were collected from the various army hospitals, than I wanted.

One or two phases create impressions, and Dr. Harbison's cases demonstrate them well. In the first place there appear to be patients with small bowel fistulas who die each year because someone depends upon replacement therapy or substitutive therapy and at the same time hopes that the local lesion will respond favorably enough to allow safe operation.

I am perfectly certain that although we have splendid substitutive therapy today, it is not nearly as completely satisfactory as we believe. The fact that, in spite of vigorous substitution, these patients continue to go downhill is evidence in favor of this viewpoint. Also, as soon as the fistula is successfully eradicated, within twenty-four hours all the vital signs have improved over and above what had been observed before closure.

A second point is, perhaps, somewhat in disagreement with Dr. Harbison's viewpoint. It is not always dangerous to incise the skin around the fistulous area. A few days of sump drainage or suction to the fistulous area, and vigorous application of skin protective therapy will frequently allow the area to get in shape so that it will withstand surgery successfully.

Resection seems to me to be the procedure of choice for the cure of small bowel fistula, if conservative nonsurgical measures fail. We have resected patients who had as many as eight fistulas, with decent morbidity and mortality rates.

Another point involves delay before surgical attack is made. One must not wait until the patient is in the pink of condition for he may allow the patient to enter a critical phase that may not be reversed. Operation consequently is performed after reasonable chemical balance and whatever gain the fistulous area may receive from a few days' vigorous treatment.

Dr. Harbison's shunting operation is obviously a great aid in treating these cases.

SICKLE-CELL ANEMIA: A SURGICAL PROBLEM

II. Further Observation on the Surgical Implications of Sickle-Cell Anemia

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THAT sickle-cell anemia is a disease of surgical interest has not been generally recognized. While the medical literature contains numerous reports since this disease was first described by Herrick in 1910,[1] relatively little has appeared in the surgical literature on this subject. Campbell, in 1935, reported on acute abdominal pain in patients having sickle-cell anemia.[2] Wilson, Patterson, and Diggs recently summarized the essential features of surgical interest exhibited by these patients and again emphasized the importance of the disease as a cause for acute abdominal symptoms.[3] The abdominal pain which these patients frequently experience may suggest the possibility of intussusception, intestinal obstruction, acute appendicitis, or perforation of a hollow viscus. Cholecystitis may also be simulated.

In a study of 142 cases of sickle-cell anemia at the John Gaston Hospital the surgical problems appeared numerous and varied. Seventeen of these patients were admitted directly to the surgical service while twelve additional individuals were admitted to other services with possible surgical diagnoses. It is the purpose of this paper to present additional problems of surgical interest as found in the central nervous system, urogenital system, bones and joints, and skin.

CHARACTERISTICS OF SICKLE-CELL ANEMIA

Approximately 10 per cent of Negroes inherit a condition known as the sickle-cell trait or sicklemia which is most easily diagnosed by observing the morphologic changes in erythrocytes when a drop of blood is sealed under a cover slip or when blood is mixed with a reducing agent such as sodium bisulfite. Most of the individuals with sickle-cell trait have no significant anemia, no evidence of increased red cell destruction, and are not incapacitated by their abnormality. Within the group of those who inherit the sickle-cell trait, approximately one in forty have sickle-cell anemia.

The diagnosis of sickle-cell anemia can be readily made by the combined history, physical examination, demonstration of the sickle-cell trait, and the usual laboratory examinations. The anemia is usually of a normocytic, normochromic type. Oval, elliptical, target, and crescent (sickle) forms are demonstrable in the stained blood smear and nuclear fragments, nucleated red cells, and diffusely basophilic cells are present. The reticulocyte count is increased. There is leucocytosis and thrombocytosis. Jaundice is usually clinically demonstrable and is of a hemolytic type in most cases, but there may be severe liver injury in addition to increased red cell destruction with

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TABLE I. PATIENTS WITH SICKLE-CELL ANEMIA INCORRECTLY DIAGNOSED AS SURGICAL PROBLEMS

Acute appendicitis	6
Possible intestinal obstruction	4
Renal colic	3
Pelvic inflammatory disease	3
Possible acute surgical abdomen	2
Acute cholecystitis	1
Mass in right lower quadrant	1
Possible ruptured appendix	1
Ruptured intervertebral disc	1
Intussusception	1
Liver abscess	1
Undiagnosed abdominal pain	1

varying degrees of regurgitant jaundice. The sedimentation rate may be normal in spite of severe anemia. The bone marrow is hyperplastic. The red cells are more resistant than normal to hypotonic salt solutions.

Other helpful diagnostic points are the occurrence of the sickle-cell trait and anemia with jaundice in other members of the family, onset in infancy with recurrent febrile episodes, pains in any part of the body, most frequently in the bones and joints simulating rheumatic fever and in the abdomen simulating acute surgical conditions, signs of central nervous system involvement, chronic leg ulcers, tendency toward hypogonadism, long extremities with relative shortening of the trunk, hepatomegaly, splenomegaly early with atrophy later, enlarged heart with systolic murmur, and roentgenographic bone changes.

The multiple and extremely varied signs and symptoms are in part due to the anemia but are also due to occlusive vascular phenomena.[4] The erythrocytes in this disease become elongated and distorted when they are subjected to conditions of reduced oxygen tension (Fig. 1). Associated with the shape change there is increased viscosity of the blood with retardation of flow.[5, 6] Any condition, local or systemic, which favors vasoconstriction, anoxia, or stasis favors sickling and thus sets up a vicious cycle with injury or necrosis of tissues resulting. At autopsy the common findings are congestion of capillaries with sickled erythrocytes, thrombosis, infarction, parenchymal degenerative changes, necrosis, and fibrosis.[7]

Between the two extremes of those who have the sickle-cell trait with no anemia and those who have severe sickle-cell anemia of a hemolytic type, there are occasional patients who have mild anemia, who develop variants of the sickle-cell syndrome late in life and who have sudden and otherwise unexplained deaths following anesthesia, alcoholic stupor, infectious states, and mild shock states.[8, 9] Many feel that surgeons, in particular, should consider the sickle-cell trait in all of the variants as a fairly common disease rather than as an unimportant hematologic curiosity and should be diligent in helping to work out missing links in our knowledge.

CEREBRAL COMPLICATIONS OF SICKLE-CELL ANEMIA

Vasospasm, vascular blockage with sickled cells, thrombosis (Fig. 2), and hemorrhagic phenomena in the brain and cord produce varied and often severe

central nervous system manifestations which simulate numerous disease entities.[10-15] Hill, Hughes, and associates of the Division of Pediatrics of the University of Tennessee have demonstrated abnormal electroencephalographic tracings in sickle-cell anemia patients with symptoms and signs referable to the central nervous system and in many patients who at the time of examination had no demonstrable evidences of cerebral involvement.[16]

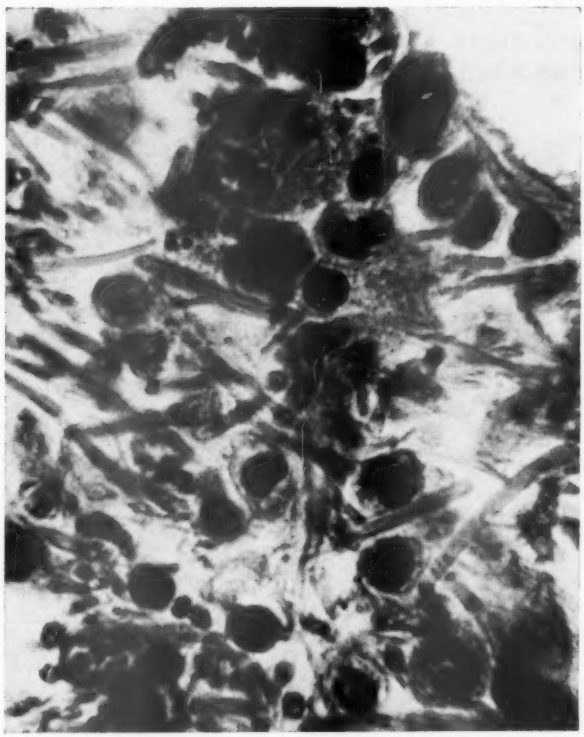

Fig. 1.—Sickled red blood cells in an autopsy specimen of bone marrow stained with hematoxylin and eosin.

Because the surgeon and neurosurgeon will be called upon to aid in the diagnosis and management of patients with severe pain, headaches, convulsions, paralyses, psychic changes, and coma, it is important for them to be aware of the potentialities of sickle-cell anemia. Also a patient with sickle-cell anemia who has acute abdominal or other surgical symptoms may have concomitant central nervous system manifestations. Awareness of sickle-cell anemia as a disease capable of involving multiple systems of the body will aid in establishing the correct diagnosis and avoid consideration of a local disease requiring surgical intervention.

Of the 142 cases studied at the John Gaston Hospital fifty-seven showed signs or symptoms referable to the central nervous system (Table II).

Headache was a frequent and bothersome complaint, having been present in twenty-six cases. Dizziness, drowsiness, and irritability were less common and more transient in nature. Faintness and recurrent syncope were seen in two patients. The more serious findings of paralysis, convulsions, coma, and stiff neck have been mistaken for meningitis, poliomyelitis, or encephalitis.

The cerebrospinal fluid from some of our patients with sickle-cell anemia who had signs of cerebral involvement were normal. In others there was an increase in manometric pressure, neutrophilic pleocytosis, and an increase in protein. Red blood cells were present in several others. The variable cerebrospinal fluid picture observed in our series and in those reported by others is due to the fact that the lesions are often small and do not involve the meninges or may be recurrent in an area of old injury in which there is local occlusion of the subarachnoid space and therefore no cellular or chemical indication of pathologic process when fluid is removed by lumbar puncture.

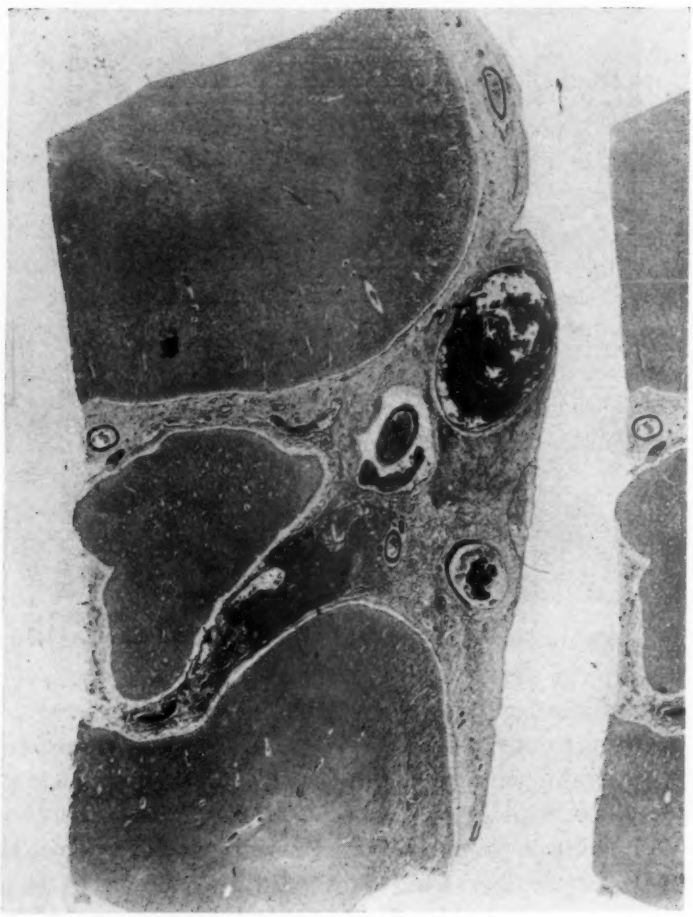

Fig. 2.—Thromboses of cerebral vessels in a patient with sickle-cell anemia seen in an autopsy specimen stained with hematoxylin and eosin.

Seven patients in our series who had central nervous system manifestations died. The most common autopsy finding was engorgement of the blood vessels with erythrocytes with focal degenerative changes. Definite thromboses were demonstrable in three cases. In the majority of the cases the maximal involvement occurred in the gray matter and meninges, but in one patient there were focal areas of hemorrhage and necrosis in the white matter. In the older lesions there was gross atrophy and scarring.[14]

TABLE II. CENTRAL NERVOUS SYSTEM SYMPTOMS AND SIGNS DUE TO SICKLE-CELL ANEMIA OBSERVED IN A STUDY OF 142 PATIENTS

Headache	26
Dizziness	6
Convulsions	5
Coma	5
Paralysis	4
Stiff Neck	3
Drowsiness	3
Irritability	3
Faintness	1
Recurrent Syncope	1
Total	57

UROGENITAL COMPLICATIONS IN SICKLE-CELL ANEMIA

The urologist may be confronted with puzzling problems in diagnosis in those patients complaining of cramping flank pain and gross hematuria. Eastland and Higgins reported a case, in 1930, in which very severe low back pain with the associated finding of red blood cells in the urine led to a consideration of renal or ureteral calculus.[17] A more complete blood study, after negative roentgenograms of the urinary tract were made, established a diagnosis of sickle-cell anemia. In 1948, Abel and Brown reported a case in which a diagnosis of renal neoplasm was made after a filling defect was demonstrated in the left kidney pelvis by retrograde pyelography in a patient having gross hematuria and cramplike pain in the left costovertebral angle.[18] Examination of the surgical specimen showed extensive necrosis of the renal pelvis caused by obstruction of renal vessels due to sickled red cells.

In our series two patients were admitted to the urological service because of flank pain and gross hematuria. Pyelography did not demonstrate any abnormality in the urinary tract and response to symptomatic treatment was prompt. It is interesting to note that many of our patients complained of passing red urine, while blood was not found on routine admission urinalyses. The dark urine noted by the patients was most likely pigment from increased hemolysis of red cells.

Four patients in our series had severe priapism. One of these patients had four hospital admissions because of this condition. While the diagnosis of priapism is obvious and its relationship to sickle-cell anemia is well established,[19, 20, 21] it is important to the urologist for he is called to treat the condition. It may result from thrombosis of vessels within the penis. In other instances it is apparently related to other factors, as one of our patients who suffered from severe priapism prior to death showed no thrombosis on serial sections of the organ at autopsy.

CASE REPORTS

CASE 1 (No. 17524).—P. M., a colored man, 28 years of age, was admitted on Nov. 25, 1946, to the urological service because of right flank pain and gross hematuria of three days' duration. Vomiting occurred with the onset of pain.

Examination revealed a slender, anemic, young man who seemed much younger than his stated age. There was an apical systolic murmur and large ulcers on both ankles. There were no other significant physical findings.

The red blood count was 2,200,000 per c.mm., the hemoglobin was 7.5 Gm., and the white blood count was 6,750 per c.mm. The urinalysis revealed albumin 3 plus and gross blood.

The patient was known to have sickle-cell anemia, having had twelve previous admissions because of this disease. His usual hospital admission was because of leg ulcers which resisted all attempts at cure including skin grafts and sympathectomy. It was thought that the hematuria was due to the sickle-cell disease, but pyelographic studies were performed to rule out the presence of stones or tumor. These were negative. Improvement was prompt after hospitalization and the urine was free of blood at the time of discharge on Dec. 1, 1946.

CASE 2 (No. 6805).—C. T., a colored male 15 years of age, was admitted to the medical service complaining of priapism of fifteen hours' duration. Two days prior to admission the patient complained of a burning sensation in the penis which was followed by a painful erection. There were two previous admissions because of this same complaint. There had been episodes of joint pains, fever, and jaundice on numerous occasions.

On examination the temperature was 99° F. and the pulse rate was 75. The liver was palpably enlarged. Scars of leg ulcers were present. The penis was very erect and painful.

The red blood count was 2,150,000 per c.mm., the hemoglobin was 6.5 Gm., and the white blood count was 22,400 per c.mm. Moist preparation revealed sickled red blood cells. Diagnosis of sickle-cell anemia with priapism was made and the patient referred to the urological service for treatment. Incision and drainage of the corpora was performed with some improvement, but the patient died after development of right upper lobe pneumonia.

BONE JOINT PROBLEMS IN SICKLE-CELL ANEMIA

The predominating complaint seen in our series of patients with sickle-cell anemia was bone and joint pain (Table III). Episodes of severe, migratory joint pains with associated fever and leucocytosis in some patients suggested rheumatic fever or infectious arthritis at the time of hospital admission. Pain may be localized in a single bone and when localized tenderness,

TABLE III. BONE AND JOINT PAIN IN SICKLE-CELL ANEMIA

Present on admission or in past history	104
Not mentioned	16
Absent	21
Pyogenic osteomyelitis	1
Total number of cases studied	142

fever, and leucocytosis are present, lead to a diagnosis of osteomyelitis and subsequent surgical operation. One child was admitted with a diagnosis of acute osteomyelitis because of tenderness over the entire left femur, fever, and leucocytosis. More detailed studies revealed the proper diagnosis of sickle-cell anemia. Another child entered the hospital acutely ill with fever, leucocytosis, swollen edematous eyelids, and tenderness over the frontoethmoid area. A diagnosis of acute ethmoid sinusitis was made and emergency surgical drainage performed. Nothing abnormal was found at exploration and

TABLE IV. X-RAY FINDINGS IN 77 PROVED CASES OF SICKLE-CELL ANEMIA

Diagnosis made first by x-ray examination	4
Definite pathology demonstrable on x-ray examination	30
No change demonstrable	43

subsequently a diagnosis of sickle-cell crisis was made. The patient had a history of recurrent bone and joint pain with associated swelling and tenderness since the age of 3 months.

Aseptic necrosis with collapse of the femoral head has been observed in these patients (Fig. 3). These findings result from the pathologic changes found elsewhere, that is, severe stasis, thrombosis with infarction, and necrosis.

Fig. 3.—Aseptic necrosis of head of femur in a patient with sickle-cell anemia.

Not all patients with sickle-cell anemia show x-ray evidence of bone changes (Table IV). The bones most likely to show changes are the skull, vertebrae, femur, tibia, and fibula. The characteristic skull changes are an increase in the thickness of the bone, absence of a well-defined outer table, osteoporosis, and radiating trabecular striations (Fig. 4). Flattening and biconcavity of the vertebral bodies may occur (Fig. 5) and there may be collapse of the vertebrae. The long bones and bones of the hand and feet may show patchy osteoporosis, but osteosclerotic lesions with replacement of marrow cavity predominate in these bones. It is interesting to note that in four of the cases seen in our series this diagnosis was suggested by x-ray findings prior to the time of blood examination.[22]

CASE REPORTS

CASE 3 (No. 68462).—A. B. F., a colored woman, aged 26 years, was admitted to the orthopedic service on Aug. 29, 1949, because of pain in the right hip of three months' duration. She had been unable to work because of this pain, but had walked by "dragging" the right foot. The past history revealed repeated attacks of joint and bone pain since childhood, episodes of abdominal pain, and repeated hospital admissions because of sickle-cell anemia. There was no history of dislocation or injury to the right hip.

Fig. 4.

Fig. 5.

Fig. 4.—X-ray film of skull of patient with sickle-cell anemia showing perpendicular striations with indistinct outer table.

Fig. 5.—X-ray film showing biconcave deformity of vertebral bodies in a patient with sickle-cell anemia.

On examination the temperature was 99.6° F., the pulse rate 96, and the respirations 24. The patient was well nourished and well developed and in no acute distress. There was a systolic murmur at the apex. Pain was elicited on hyperflexion of the right hip. Hyperextension of the right hip could not be carried out. There was a swinging type gait with a right leg drag reducing hip movement to a minimum.

The red blood count was 2,320,000 per c.mm., the hemoglobin was 8.5 Gm., and the white blood count was 19,350 per c.mm. The urinalysis was negative.

Roentgenograms revealed some decalcification of the upper end of the right femur with considerable cortical erosion involving the femoral head. These findings were interpreted as due to a pyogenic process and a diagnosis of acute infectious arthritis was made.

When additional x-ray studies demonstrated typical sickle-cell anemia changes in the lumbar vertebrae and further observations failed to substantiate the diagnosis of an acute infectious process, the hip changes were considered due to aseptic necrosis caused by sickle-cell anemia.

CASE 4 (No. 94522).—F. B., a colored girl, aged 17 years, was seen in the orthopedic outpatient clinic on Aug. 26, 1949, because of pain in the left hip on movement of one year's duration. She was a known sickle-cell anemia patient and had been hospitalized on two occasions because of leg ulcers.

On examination the temperature was 99° F. and the pulse rate 96. The patient was slender and anemic appearing with long, thin extremities. The left hip appeared enlarged and the left leg was shorter than the right. Ulceration was present over the anterior aspect of the lower left leg.

The red blood count was 3,000,000 per c.mm., the hemoglobin was 9.5 Gm., and the white blood count was 15,000 per c.mm. The urinalysis was negative.

Roentgenograms revealed irregularity and flattening of the head and marked deformity of the capital femoral epiphysis of the left extremity, osteoporosis about the head and neck and trochanters, and also about the inferior portion of the acetabulum. These findings were interpreted as typical of those usually seen in aseptic necrosis.

Additional x-ray studies showed osteoporosis in the parietal region of the skull, decrease in height of the bodies of all the lumbar and the lower thoracic vertebrae with widening of the intervertebral spaces, and osteoporosis in the femora with coarsening of the trabeculations.

A diagnosis of sickle-cell anemia was made.

LEG ULCERS

Since the earliest reports of this disease leg ulcers have been described as a common finding.[23, 24, 25] In our own series ulcers or ulcer scars were noted in forty-two patients. In our experience these lesions are more likely to develop in adults than in children. These ulcers appeared most commonly about the ankle and lower shin, although they also have been observed on various parts of the leg. They may be single or multiple, unilateral or bilateral, and are usually "punched-out" in appearance. They are characterized by their chronicity and resistance to treatment. One of our patients whose predominant complaint was leg ulcers has had twenty-one hospital admissions because of this condition. Ointments, bed rest with elevation of the extremities, pressure dressings, excision with skin graft, and sympathectomy were used in attempts to cure these ulcerations. Temporary healing has resulted after long periods of hospitalization only to be followed repeatedly by a recurrence of the ulceration in a relatively brief period of time.

SUMMARY AND CONCLUSIONS

Sickle-cell anemia is a disease with protean manifestations which is characterized by vascular occlusive phenomena affecting all organs of the body and producing abdominal, central nervous system, bone and joint, urological, and skin lesions which are of interest and importance to the surgeon.

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DISCUSSION

DR. R. BOWERS.—Any of us who handle Negro patients should know about this disease. If you see only a few Negro patients, you are likely to misdiagnose and perform an unnecessary operation, unless the disease is borne in mind. We are grateful to Dr. Wilson and the group at Tennessee for bringing this out so clearly in a large number of cases.

The literature alludes to the fact that these symptoms are seen in Negro people, usually young Negroes who are not older than 20 years of age. We have had five cases in adults who were older than 20 years. Dr. Wilson did not stress the fact that most of his cases occurred in children. Three of our cases were between ages 25 and 30, and two were over 30. The last patient died on Monday of this week. He was 39 years old and autopsy verified the diagnosis.

I rise to call attention to the existence of this disease in the adult, and to fortify the opinion that an awareness of the presence of the disease must exist or diagnosis will not be forthcoming.

Of our five cases, two were subarachnoid hemorrhages, one was an abdominal case suspected of impending perforated ulcer but was not operated because of sickle-cell anemia. He has been in and out of the hospital four or five times, and we anticipate more abdominal attacks until death from sickle-cell anemia finally overtakes him. A fourth patient died with necrosis of the liver and infarcts in the spleen and kidneys—thromboses due to sickle-cell anemia. In this case, however, beside thrombosis we do see arterial changes suggestive of periarteritis nodosa. The fifth case mentioned earlier is undoubted sickle-cell anemia in a Negro man, 39 years of age. I would like to make a few remarks about the abdominal findings, because there is something fairly typical about them. Dr. Wilson mentioned priapism. Our fifth case showed priapism, abdominal pain, jaundice, and demonstrated cerebral symptoms early.

The history is likely to be a confused one due to cerebral involvement; at first it seems that the patient is failing to cooperate, but the truth lies in the fact that he often is unable to cooperate. Dr. Wilson's final caption was cerebral accidents and certainly cerebral thrombosis is common in the disease as was demonstrated in our fifth case.

But what I have seen of these abdomens is this: As one approaches the patient for physical examination of the abdomen, one notices the patient's reluctance in submitting to abdominal palpation. He immediately grasps your hand and tries to prevent you from carrying out the examination. This was demonstrated so well in our fifth case, because it was extremely difficult to deny exploration with accuracy. Each time the patient grabbed the examiner's hand.

During the first excursion of abdominal palpation, one is often impressed with seeming rigidity. However, on the second excursion there is doubt, and on the third excursion when the patient's attention is diverted, one can be more certain that actual rigidity is not present. In the fifth case, bearing in mind these observations, we did not operate. At post-mortem examination there was mottling of the small intestine, but the man died of cerebral thrombosis.

Dr. Wilson has done much to establish an awareness of this disease. It occurs in Negroes and can occur in adults as we have seen in our cases at Kennedy Hospital.

DR. E. A. CAMPBELL.—I should like to add one more word of commendation for this excellent and very thorough study, and to reiterate the fact that this disease, like others in which thromboses are frequent features, can manifest itself in a great variety of ways.

Among eleven cases observed in the Albany Hospital, two children were found to have cerebral thromboses; no cause other than sickle-cell anemia was found.

I would like just to take issue with Dr. Bowers concerning the clinical picture of the acute abdomen in these individuals, because I am not sure that one can always be positive that the patient does not have some other disorder which requires surgery.

These individuals are subject to all the other disorders which curse mankind, in addition to their sickle-cell anemia. I think it has to be borne in mind that they are not immune to other surgical emergencies.

DR. E. F. PARKER.—I just want to enlarge upon one feature, in addition to congratulating Dr. Wilson on his excellent presentation in calling attention to conditions simulating acute abdominal emergencies requiring operation.

As Dr. Campbell added, people with sickle-cell trait, with or without anemia, are subject to all other diseases, and we see them very commonly. Dr. Wilson mentioned an examination of the blood for sickle-cell trait which is routine in our hospital throughout the Negro wards.

It is a strange and remarkable fact that in operations on people with the sickle-cell trait, it apparently does not cause any trouble; and even in patients who die from some other disease, it is interesting that the sickle-cell trait, which can be diagnosed by the pathologist, is very seldom a major cause of death.

In a person with 100 per cent sickling of the cells in twenty-four hours or any degree of sickling in seventy-two hours, the only precaution taken is to be doubly certain that they do not suffer any degree of anoxia during the operation, to try to prevent the development of the crisis so well described by Dr. Wilson.

NECK DISSECTIONS IN CANCER OF THE LOWER LIP

Five-Year Results in 179 Patients

John Modlin, M.D.,* Columbia, Mo.

DESPITE the frequent occurrence of cancer of the lower lip, the management of lymph node metastases from these lesions remains a controversial subject. The majority of clinicians are agreed that neck dissection is the preferred method of treatment of most patients with such metastases, notwithstanding the occasional exponent[1] of irradiation methods. Agreement is lacking, however, concerning the optimum time of performance of neck dissection, discussion[2-13] of the problem having centered around the merits of the so-called "prophylactic" or early neck dissection versus the therapeutic or delayed neck dissection.

It is the purpose of this paper to present the incidence of lymph node metastases, together with the results of treatment, in 179 patients with cancer of the lower lip who have been carefully followed at The Ellis Fischel Cancer Hospital for periods of 5 years or more.

MATERIAL

In the group of 179 consecutive patients with cancer of the lower lip examined prior to June, 1944, there were 13 patients who were not treated for cure. In this group are included those patients who refused treatment, who were considered too far advanced for treatment, or who were treated with palliative intent alone. A 100 per cent follow-up has been obtained in all cases, and although several patients failed to return at regular intervals, the final 5-year result of treatment is known in every case.

Since only 2 prophylactic dissections were performed in the entire group of 179 patients, there has been an excellent opportunity to determine not only the incidence of cervical metastases from cancer of the lower lip, but also the curability of therapeutic neck dissections in those patients who developed lymph node metastases while undergoing follow-up.

INCIDENCE OF METASTASES

In Table I is illustrated the percentage of metastases in all patients with cancer of the lower lip who were examined in The Ellis Fischel Cancer Hospital prior to June, 1944. The total incidence of metastases was 20 per cent of 179 patients (patients with metastases on admission and patients who developed metastases during follow-up), but only 9.6 per cent of 156† patients admitted without evidence of metastases subsequently developed positive nodes.

RESULTS OF THERAPEUTIC NECK DISSECTIONS

Thirty-two neck dissections were performed in the group of 179 patients. Of these, 2 were prophylactic in type and proved to have no evidence of

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†There were 158 patients admitted without evidence of metastases; however, two had "prophylactic" neck dissections.

TABLE I. INCIDENCE OF METASTASES

METASTASES	NUMBER OF PATIENTS	PER CENT
No metastases on admission	158	88.8
Metastases on admission	21	11.7
Metastases during follow-up	15	9.6
Total metastases (5 year follow-up)	36	20.0
Total patients	179	100.0

metastases on histologic examination. Thirty operations were considered to be therapeutic in type, but 5 of these also proved to have no metastases on careful histologic examination, thus leaving 25 patients who had therapeutic dissections for histologically proved metastases. Twelve patients had metastases when first seen; 4 in this category were so far advanced that concomitant resection of the mandible was necessary. Thirteen of the 25 patients who had histologically proved metastases lived 5 years or longer without evidence of disease, an absolute 5 year cure rate of 52 per cent (Table II).

TABLE II. FIVE-YEAR RESULTS OF THERAPEUTIC NECK DISSECTIONS (INCLUDING PATIENTS WITH METASTASES ON ADMISSION)

Total therapeutic neck dissections	30
Total with positive nodes	25
5 year absolute cures	13/25 or 52%

The fate of 15 patients who developed metastases during follow-up is shown in Table III. Despite the fact that 2 patients developed inoperable metastases during this period, 8 patients, or 52 per cent, are alive and free of disease 5 years or longer.

TABLE III. FATE OF PATIENTS DEVELOPING METASTASES DURING FOLLOW-UP

	NUMBER	PER CENT
Total patients with no metastases on admission	158	100.0
Total patients developing metastases during F. U.*	15	9.6
Patients developing inoperable metastases during F. U.	2	1.2
5 year absolute cures, therapeutic neck dissection	8/15	53.0

*F. U., follow-up period.

There was 1 postoperative death in the series of 32 neck dissections. This patient has been included as a failure of therapeutic neck dissections in the computation of the 5-year absolute cure rate.

DISCUSSION

It is generally accepted that a high percentage of the primary lesions in patients with cancer of the lower lip can be successfully controlled by both surgical and irradiation methods, the type of treatment in a given clinic often depending on individual training and experience. As pointed out by Slaughter,[14] the control of metastases from cancer arising in the head and neck is of prime importance as far as the permanent control of these lesions is concerned, a fact that is frequently overlooked until incurable metastases have developed. Since lymphatic spread from cancer of the lower lip is be-

lieved to occur by a process of embolization rather than by direct permeation along lymphatic channels,[15] the management of lymph node metastases from cancer of the lower lip is a separate but fundamentally important portion of the treatment of this disease.

A study of the literature of the past 15 years reveals a wide diversity of opinion regarding the management of lymph node metastases from cancer of the oral cavity. Erroneous conclusions have been derived from inadequately followed groups of patients and the lack of individualization of patients according to the site of origin of the primary lesions has also caused confusion. Also, while the accuracy of the clinical evaluation of cervical metastases increases with experience, a variable margin of error does exist, and statistical studies based on the assumption that palpable nodes represent definite metastases have added to the complexity of the problem. In the present series, the majority of neck dissections were performed after clinical evidence of metastases was demonstrated by competent clinicians, yet 5 patients proved to have histologically negative nodes following neck dissections.

The use of the term "prophylactic" neck dissection is unfortunate, since it implies prevention of cervical metastases. Although Judd and Beahrs stated in a recent report[9] that the prophylactic neck dissection prevents the development of metastases "by blocking off the lymphatics," it would seem nearer the truth to define the early elective or prophylactic neck dissection as the removal of lymph nodes in which metastases have already developed but which have not sufficiently enlarged to be detected by clinical examination. The therapeutic neck dissection, on the other hand, implies removal of lymph nodes after metastases have enlarged sufficiently to become clinically evident.

The essence of the problem concerning the timing of neck dissections in the treatment of cancer of the lower lip lies in: (1) the incidence of later metastases in patients who present no clinical evidence of lymph node metastases when first seen,[7] and (2) the comparative results of prophylactic (early) neck dissections and therapeutic (delayed) neck dissections in patients with proved metastases. Confusion has resulted from the failure to differentiate between patients presenting definite evidence of metastases on admission and those without evidence of metastases at that time. It is obvious that the question of early or delayed neck dissection arises only in the latter group of patients, while patients with already manifest metastases on admission are candidates for the therapeutic operation only. In addition, comparisons between the efficacy of the early and delayed operations have often been made[19] on studies of the results in all patients undergoing neck dissection whether or not histologic evidence of lymphatic metastases is found in the operative specimen. Since only a small percentage of patients with cancer of the lower lip will ever develop metastases regardless of whether or not neck dissection is done, it is evident that evaluations of the curability of early and delayed neck dissections should include only those patients with histologic proof of metastases in the operative specimen.

In the present series of 179 patients with cancer of the lower lip, 36, or 20 per cent, exhibited cervical metastases either on admission, or during follow-up. As previously emphasized, however, the crux of the problem concerning the optimum time of performance of neck dissection is limited to those patients who have no evidence of metastases at the time of treatment of the primary lesion. If an appreciable percentage of such patients subsequently develop metastases, there is little argument against the performance of early neck dissections. In this series, 9.6 per cent of 156 patients developed metastases during a period of observation of at least 5 years (Table I). Other authors have reported similar rates of metastases (Table IV). Although the present-day operative risk of neck dissections is small, it would seem illogical to

TABLE IV. INCIDENCE OF METASTASES; PATIENTS WITHOUT EVIDENCE OF METASTASES ON ADMISSION

AUTHORS	TOTAL PATIENTS	SUBSEQUENT METASTASES	PER CENT
Martin	375	30	8.0
Figi	549	91	16.0
Richards	244	3	1.0
Taylor and Nathanson	400	36	9.0
Totals	1,568	160	10.0

perform 90 operations on patients who will never develop metastases in order to benefit 10 patients with early cervical metastases. This seems particularly pertinent since the curability following therapeutic neck dissections for patients with cancer of the lower lip in this series compared favorably with the quoted curability rates for the elective prophylactic neck dissection performed in patients with histologically proved metastases (Table V).

TABLE V. FIVE-YEAR CURES IN PATIENTS WITH PROVED METASTASES

AUTHORS	NUMBER OF PATIENTS	PROPHYLACTIC (PER CENT)	THERAPEUTIC (PER CENT)
Eckert and Petry	57	42	
Martin	35		31
Taylor and Nathanson	10	57	
Ellis Fischel Cancer Hospital	25		52

Careful study of all operative specimens following therapeutic neck dissections for cancer of the lower lip at The Ellis Fischel Cancer Hospital has revealed an important factor which may account for the apparent equal curability of the prophylactic and the therapeutic procedures. From a study of Table VI, it can be seen that 84 per cent of 52 neck dissection specimens had not over 2 nodes involved, and that 57 per cent had only 1 involved node.

TABLE VI. NUMBER INVOLVED LYMPH NODES IN 52 THERAPEUTIC NECK DISSECTIONS

NUMBER OF NODES	NUMBER OF PATIENTS	PER CENT
1	30	57.7
2	14	26.9
Multiple nodes	8	15.3

It is emphasized that a careful search was made for lymph nodes in all specimens, with as many as 90 lymph nodes being found in a single case, and the number of involved nodes is considered to be quite accurate. It would appear that there is, in general, a tendency for metastases from cancer of the lower lip to remain localized in 1 or 2 nodes for a considerable period of time, with only a small percentage of patients developing multiple lymph node involvement at an early stage. This fact may explain the comparative curability of delayed or therapeutic dissections.

If early neck dissections are not routinely done, an efficient follow-up system is mandatory in order to detect metastases at an operable stage. Two patients in this series presented inoperable metastases after return to the hospital following several broken appointments. These are considered to be failures of therapeutic dissections, since the routine performance of early neck dissection might have prevented this occurrence. The possibility of this happening is an argument in favor of the policy of the routine performance of early prophylactic neck dissections, but it should be recalled that the loss of these 2 patients (1.3 per cent of the group of 156 patients admitted without metastases) can be balanced against the expected operation mortality if routine early neck dissections had been done.

If prophylactic neck dissections are not routinely done, it would be of help to be able to predict which patients have a higher chance of development of metastases during follow-up. Such factors as anaplasia, previous inadequate treatment, and large size of the primary lesion have been noted by others[3, 7, 12] to increase the likelihood of metastases. These factors have been evaluated* in the present series of cases and the results are summarized in Table VII. The method of histologic grading, as used in this series, is somewhat at variance with that advocated by Broders. Not only are the quantitative aspects of cell differentiation evaluated, but the growth pattern is also estimated. The latter is considered in terms of the size of the tumor masses as seen in single sections, and in any tendency to circumscription. The resultant impression is categorized into two divisions which could be labeled "of average degree of malignancy" and "a more than average degree of malignancy." These are, for simplicity, called grade 1 and grade 2. While a positive correlation between our grade 1 and Broder's grades 1 and 2, and between

TABLE VII. INFLUENCE OF ANAPLASIA, PREVIOUS INADEQUATE TREATMENT, AND LARGE SIZE OF PRIMARY LESION

TOTAL	PREVIOUS TREATMENT	SEZE RELATIVE TO 3.0 CM.	GRADE		METASTASIS ON ADMISSION	LATE METASTASIS
	None	Less	1	105	1	6
		119	2	14	2	1
	129	More	1	3		1
161		10	2	7	2	2
	Inadequate	Less	1	17	2	
		22	2	5	3	
	32	More	1	8	3	1
		10	2	2	2	

*By Dr. Richard Johnson, pathologist, The Ellis Fischer Cancer Hospital.

our grade 2 and Broders' grades 3 and 4 undoubtedly exists, such a comparison is not strictly valid. Satisfactory evidence of the utility of our method is obvious in Table VII. Of 131 cases labeled grade 1, only 14, or 11 per cent, showed metastases. Of 28 in grade 2 category, 12 had metastases, a frequency of 43 per cent. It is emphasized that the grading was done without prior knowledge of the clinical evolution of these cases. However, as illustrated in Table VII, 9 of the 28 patients with grade 2 lesions had metastases on admission and since only 3 of the remaining 19 patients with grade 2 lesions subsequently developed metastases (15.7 per cent), it is apparent that the grade of the primary lesion per se would not have been of significant aid in the decision concerning early neck dissection.

A history of previous inadequate treatment of the primary lesion was found in 32 patients, and 11 or 34 per cent developed metastases either on admission or during follow-up. This would seem to favor the performance of early neck dissection in such patients. However, all but 1 of the 11 patients had metastases when first seen at the hospital, and only 1 of 22 patients with a history of previous inadequate treatment and with no palpable nodes on admission later developed metastases during a 5 year period of follow-up (Table VII). Thus, early neck dissection in this group of 22 patients would have yielded only 1 patient with occult metastases. Those primary lesions over 3 cm. in size also exhibited a higher rate of metastasis (Table VII). However, there were only 20 lesions of this size in the entire series. Of these, 7 had metastases on admission. Although 4 of the remaining 13 patients (30 per cent) developed metastases during follow-up, it is probable that the number of cases is too small to be statistically significant.

Of 42 patients who showed one or more of the 3 criteria enumerated (anaplasia, previous inadequate treatment, or large size of the primary lesion), 5 (12 per cent) developed late metastases. It is concluded, therefore, that, while the preceding factors account for a higher total incidence of metastases from cancer of the lower lip, their usefulness in selecting patients for early or prophylactic neck dissections (that is, patients who come to the hospital without palpable nodes and who exhibit any of the previously mentioned factors) is, at least, doubtful. Consideration should be given to performance of the early or prophylactic dissection in those patients where suspicion exists that regular follow-up cannot be maintained. Taylor and Nathanson[11] have pointed out that "Adequacy of follow-up is the determining factor in the decision for or against 'prophylactic' neck dissection in many cases." For the first 18 months after treatment of the primary lesion, follow-up examinations should be performed at 1 month intervals whenever practicable. At The Ellis Fischel Cancer Hospital, a 2-month period between examinations is allowed due to the long distances travelled by most of the patients. Of the 15 patients who developed metastases during follow-up, 10 are known to have occurred within 6 months after treatment of the primary lesion, 14 within 1 year, and 1 after 30 months.* From the aforementioned data, it would appear

*This patient returned after 16 broken appointments and the history concerning the time of appearance of the metastatic lesion is considered unreliable.

that the greatest vigilance should be exercised during the first 18 months of follow-up after treatment of the primary lesion. If such a follow-up system cannot be maintained, there is no doubt that a higher percentage of early neck dissections is in order. It can be pointed out again, however, that only 1 in 10 patients who have no metastases when first seen, will subsequently develop them, hence the expected loss from metastases in this group (without follow-up of any kind) should not be excessive.

If the incidence of metastases from cancer of the lower lip is as low as is indicated in the present series of cases, this fact, coupled with the curability of about 50 per cent for therapeutic neck dissections, should yield a high over-all 5 year cure rate in all patients with cancer of the lower lip. This proves to be the case (Table VIII), the 5 year absolute cure rate being 64.7 per cent, the net 5 year cures being 84.5 per cent. (The difference between the absolute and net 5 year results is due largely to deaths from intercurrent disease.)

TABLE VIII. OVER-ALL FIVE-YEAR RESULTS OF TREATMENT, 179 PATIENTS

5 Year absolute cures	115 patients	64.7%
Net 5 year cures		84.5%
Indeterminate patients		
Refused treatment or palliation	5	
Died intercurrent disease	38	
Lost to follow-up	0	
Total indeterminate	43	
Determinate patients	136	
Failures		
Died of cancer	16	
Died other causes, cancer present	5	
Total failures	21	
Successful results	115	
Net 5 year cures	115/136 or 84.5%	

SUMMARY

1. The controversial issue of early versus delayed neck dissections for cancer of the lower lip should be judged on (1) the incidence of later cervical metastases in patients who have no evidence of such metastases when admitted for treatment of the primary lesion, and (2) the comparative curability of early and delayed neck dissections in patients with histologic evidence of metastases in the neck dissection specimen.

2. Approximately 10 per cent of 156 patients admitted for treatment of cancer of the lower lip without clinical evidence of metastases subsequently developed metastases during a 5 year period of follow-up; of these, approximately one-half were salvaged by delayed or therapeutic neck dissections.

3. The 5 year absolute cure rate of 179 patients with cancer of the lower lip examined at The Ellis Fischel Cancer Hospital prior to June, 1944, was approximately 65 per cent. The net 5 year cure rate was approximately 85 per cent.

4. Provided that an efficient follow-up system is maintained, the data in this series of cases indicate that the routine performance of early or prophylactic neck dissection in patients with cancer of the lower lip is not justified.

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DISCUSSION

DR. D. P. SLAUGHTER.—I should like to congratulate Dr. Modlin. I think that is the highest figure of cure rate for neck dissections for positive lymph nodes that I, personally, have seen. I am in complete agreement with his point of view against prophylactic neck dissection. That applies entirely to cancer of the lip. I do not think the same arguments are applicable in quite the same degree to cancer of the tongue, as here the timing is of extreme importance. Even in a therapeutic neck dissection it should be delayed and not done at the same time the primary is removed unless an excision and dissection in continuity is done. That is the same situation, of course, as a radical mastectomy, where you take out the primary regional nodes and the intervening lymphatics. That is a much more difficult thing to do in intraoral or lip cancer, where we usually have to leave a block of tissue in between. Even if a therapeutic dissection is indicated, that is, if nodes are present when the patient is first seen, they must not be removed until the primary is completely eradicated.

That is another argument against prophylactic neck dissection because we are never certain we have eliminated the primary, whether it is treated by surgery or irradiation.

I would like to ask Dr. Modlin to define what he means by neck dissection. There is a world of difference between a submaxillary or suprahyoid and bilateral suprahyoid or supraomohyoid, and a radical neck dissection.

My practice is, when a lesion is in the midline, or if there are bilateral metastases, to do a radical neck on one side, and supraomyhyoid at the same time and through the same incision on the other side.

If the lesion primarily does not involve the midline, and if there is even one node involved, I always do a radical neck dissection now if the patient is a reasonable surgical risk—from sad experience of having to convert many limited dissections into radicals.

DR. J. MODLIN.—In answer to Dr. Slaughter's question concerning the type of neck dissection indicated in patients with metastases from cancer of the lower lip, I thought that a breakdown of the small number of dissections performed in this series was not warranted. Despite the fact that the majority of patients with metastases had not over 2 involved nodes, I would certainly agree that the patient who has definite evidence of metastases in the submaxillary group of nodes should have a total neck dissection, and this is our current practice.

The problem of the patient with bilateral metastases with greater enlargement on one side is a difficult one to answer. Such cases should be individualized and, provided that the general condition of the patient permits, I would think that the total neck dissection should be performed on the side with the greatest involvement with a supraomohyoid neck dissection on the opposite side at the same time.

PERMANENT CAMOUFLAGE OF CORNEAL SCARS USING INSOLUBLE TATTOO PIGMENTS

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APPROXIMATELY three years ago, we presented a technique to camouflage corneal scars permanently by injecting insoluble pigments.[1] It is our feeling that any successful procedure reported with enthusiasm, as was the original report, should be followed by later observations. In doing so, the indications and scope of the procedure may then be determined more accurately.

The first recorded case of purposeful tattooing of the eye occurred in 1870, when von Wecker[2] introduced India ink into a scarred cornea. He had previously noted "that in workmen wounded by the explosion of mines, the grains of powder remained in the cornea without producing any remarkable haziness in the surrounding tissue." The first American cases of corneal tattooing were presented by Calhoun[4] and Williams[5] in 1873. Since the procedure did not have the importance of those capital operations which preserve or restore vision, it was temporarily abandoned until 1925, when Knapp,[6] using gold chloride, attempted to stain a corneal scar. Other investigators[7-10] attempted to use various chemicals, but these for the most part resulted only in failures which led Pischel,[22] in 1930, to state that "Most results have been disappointing, both to the patient and to the surgeon. A fine black pupil achieved with much effort and some pain becomes, in the course of a few days, woefully light again. Therefore, any improvement in technique or results must be welcomed." This challenge was accepted, with results which will be recorded in this presentation. Since Pischel's[22] statement appeared twenty years ago, only a single article,[3] besides our own,[1] has appeared in the American literature.

In recent years, keratoplasty has attracted a great deal of popular interest and, as a result, many blind persons have sought a corneal transplant operation hoping that their sight could be restored. Unfortunately, however, the majority of these people are doomed to disappointment because most cases of blindness are due to causes other than corneal scars. Among the types of corneal opacities covering the pupillary area, some are susceptible to treatment by corneal transplantation, which gives the best results as far as improvement of vision is concerned. Other opacities are unfavorable or are not acceptable because of excessive density of the scar or pronounced superficial vascularization, which would render the transplant nebulous or opaque. What

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then can be done to relieve or correct this conspicuous deformity in those patients who are not acceptable candidates for a corneal transplant? We believe that tattooing, alone, or combined with iridectomy, is the procedure of choice.

PHYSIOLOGIC PROPERTIES OF THE CORNEA

The cornea differs from all other tissues of the body in several important ways. Fischer[11] has shown that the cornea normally can utilize oxygen directly from the air. Thus the respiration of the whole structure can be studied supravitally without slicing or maceration.

Wounds of the corneal epithelium have been shown by Puchkovskaya[12] to heal in the isolated organ as long as two days after its removal from the body. Cogan and Kinsey[13] have demonstrated that corneal pieces possess an extraordinary capacity to swell when immersed in various aqueous solutions, including blood serum, regardless of the tonicity of the solution, the nature of the solvent, or the hydrogen ion concentration. This property of imbibing fluid over and above the normal content—this characteristic of being maintained normally in a deturgesced state—distinguishes the cornea, in general, from other tissues. Thus, in order for the cornea to remain transparent, it must be maintained in a deturgesced state. It is so maintained by continuous removal of water through differences in the osmotic pressure.[13] The effectivity of the osmotic pressure in turn depends on the presence of the semipermeable membranes of the cornea, the anterior and posterior elastic membranes (Fig. 1). At the limbus, where these membranes terminate, the stroma becomes relatively hydrated and opaque, thus accounting for the abrupt optical transition from the transparent cornea to the opaque sclera for which there is no histologic counterpart. Removal or destruction of one of the semipermeable membranes results in swelling and opacity of the cornea.[16] The cornea then approaches the sclera in its optical properties.

It is quite amazing that the conspicuous optical difference which exists between the cornea and sclera has never been shown to have any histologic counterpart. The stroma of one emerges into that of the other at the limbus without any abrupt transition corresponding to the change from transparent to opaque portions of the corneoscleral coat. That the swelling and optical peculiarities of the cornea might be correlated has been suggested. It has long been known that when the cornea takes up water it becomes opaque.[15] On the other hand, when the sclera loses water, it becomes transparent.[14] The optical differences between the cornea and sclera would appear to be associated with their relative state of hydration. It is known that the normal cornea is maintained in an extraordinary compact state by means of potent osmotic forces,[13] and that, following trauma, the cornea swells, which allows the tissue spaces to become loose. Since the normal cornea is not provided with blood vessels, bleeding rarely, if ever, occurs in the normal cornea. We have observed, however, that some superficial bleeding may occur in a corneal scar which is vascularized or which is swollen, when an attempt is made to tattoo it.

ANATOMIC CONSIDERATIONS OF THE CORNEA

The cornea is the clear, transparent, anterior portion of the external coat of the eyeball. It is nearly circular, but is slightly wider in the transverse than in vertical direction. Its radius of curvature is somewhat shorter than that of the sclera. The junction of these two layers, the limbus, is in complete

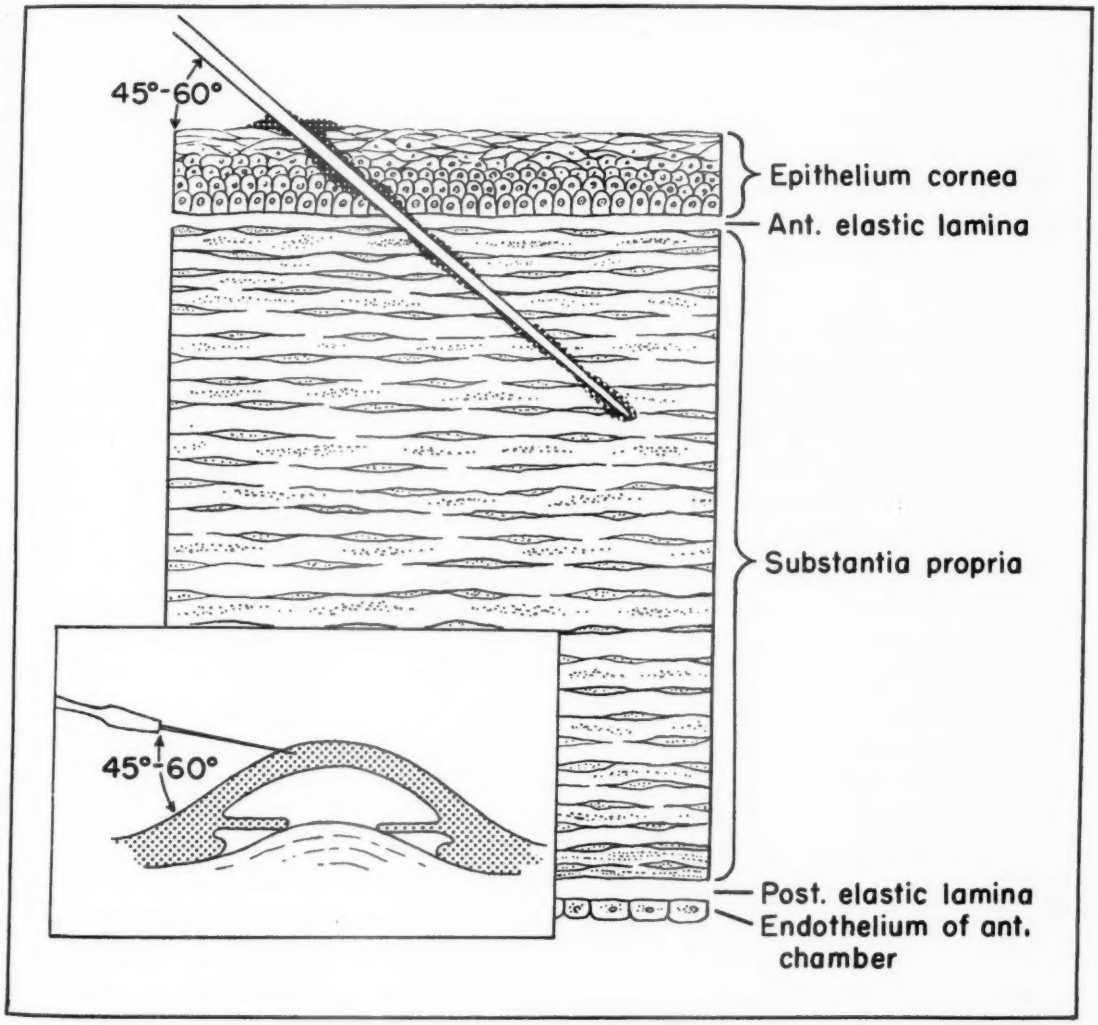

Fig. 1.—Diagrammatic representation of the various layers of the cornea and method of pigment injection. Since the cornea has neither blood vessels nor lymphatics, there is no dispersion or diffusion of pigment if it has been injected into the substantia propria. Pigment that has been injected too superficially and only into the corneal epithelium may be desquamated and lost during the healing process. The tattoo needle should be held at an angle of 45 to 60 degrees so that an oblique line of pigment will result. As the needle is inserted into the cornea, some pigment will remain on the surface, as illustrated. So that one will not be guided falsely, this excess pigment should be flushed or wiped away using cotton wisps. Tattooing should be continued until the area to be concealed is quite homogeneous.

continuity. The cornea is composed of five layers (Fig. 1), from without inward: *A*, layer of epithelial cells; *B*, Bowman's membrane; *C*, corneal stroma; *D*, Descemet's membrane; *E*, a layer of endothelium.

The epithelium covering the front of the cornea (Fig. 1, *A*) is of stratified variety, formed of flattened, scaly epithelial cells superficially of polygonal

cells beneath these, and of columnar cells most deeply. Practically it is part of the bulbar conjunctiva.

Bowman's membrane (Fig. 1, *B*), the anterior elastic lamina, is a thin, homogenous membrane which separates the corneal epithelium from the proper substance of the cornea. Although usually described as a separate membrane, it is really a part of the corneal substance, and when magnified highly it is seen to be composed of fine fibers which are intimately connected with the subjacent layer.

The stroma (Fig. 1, *C*), the substantia propria of the cornea, is the thickest layer, and is formed of connective tissue arranged in lamellae, the planes of which are parallel to the surface of the cornea. These lamellae are connected with one another. The ultimate fibrils of which the lamellae are composed, as well as the different bundles of fibrils forming the lamellae, are held together by means of a transparent cement substance. The corneal substance is traversed by a system of spaces or lacunae situated in the cement substance separating the laminae, and sending off prolongations in every direction; these form small canals by means of which the lacunae of the same plane and those placed above and below communicate. The spaces are filled with branching cells, corneal corpuscles, the branches of which pass into the small canals and communicate with adjoining cells. These cells are known as fixed corpuscles in contradistinction to the leucocytes which move about and are called wandering cells of the cornea. The proper substance of the cornea passes uninterruptedly into the sclera.

Descemet's membrane (Fig. 1, *D*) (the posterior elastic lamina) is a thin, firm, structureless, transparent, and highly elastic layer, placed posterior to the proper substance of the cornea. At the periphery of the cornea it passes over into the radiating bundles of elastic fibers which form the meshwork of the angle of the anterior chamber (ligamentum pectinatum). Posteriorly, and next to the anterior chamber, is a single layer of flattened, hexagonal cells. the endothelium (Fig. 1, *E*).

The cornea is not provided with blood vessels. The capillary loops from the ciliary vessels form a ring around the circumference of the cornea.

Nutrition of the cornea is provided for by the system of canals and channels just described. However, no one has ever demonstrated the presence of lymphatics in the cornea.

The cornea is richly supplied with nerves from the ciliary branches of the trigeminal.

The line between the cornea and sclera is known as the limbus.

EXPERIMENTAL DATA

Since attempts by other investigators[7-10] to stain the cornea had failed, the problem was taken to the experimental laboratory. We were first desirous of learning whether certain metallic salts would stain the intact cornea in the experimental animal, and, if staining occurred, what color was produced, and how long it would remain.

Albino rabbits were selected because their eyes are approximately the size of human eyes and the iris is light in color. Concentrations of 2 and 5 per cent solutions of gold chloride, platinum chloride, gold cyanide, silver cyanide, potassium ferrocyanide, and ferric chloride were used respectively to flood the eyes of each set of animals for ten minutes. Following this the nictitating membranes and lids were held open for an additional fifteen minutes to allow for the reduction of the metallic salt. Following recovery from the anesthesia, there was slight injection of the cornea and conjunctiva, which may have been due to mechanical trauma. However, there was no staining of the cornea, conjunctiva, or nictitating membrane in any of the rabbits during the three-week period of observation.

To determine whether these same chemical agents would stain the denuded cornea, all or part of the cornea was removed from another group of twelve rabbits. This was performed by using a Keyes cutaneous punch or a corneal trephine to circumscribe the test area, following which all of the corneal epithelium within this area was removed meticulously. A 2 per cent solution of each agent was dripped into the eye denuded of its cornea, following which the eyes were exposed to the air for an additional fifteen minutes, before the animals recovered from the anesthesia, to allow for the reduction of the metallic salt. The eyes of the animals were observed several times daily thereafter. On consecutive days, another pair of rabbits were similarly operated upon, using, respectively, a 2 per cent and a 5 per cent solution of platinum chloride, gold cyanide, silver cyanide, potassium ferrocyanide, and ferric chloride.

RESULTS

Although the 2 per cent solution of gold chloride produced a brown discoloration of the denuded area of cornea, nevertheless, there was considerable vascularization of the cornea present within two weeks, rndering the regenerated corneal nebulous. The 5 per cent solution caused a severe iritis. And although a brown color was formed, it was soon covered by a gray-white coagulum, which persisted for about ten days. When the epithelium had regenerated, the denuded areas were opaque and no brown discoloration was visible. While platinum chloride produced a light discoloration immediately, it was not visible after about one week. Gold and silver cyanide evoked a severe reaction in the eyes of all animals. A cloudy cornea developed in each instance, without discoloration. Potassium ferrocyanide and ferric chloride produced only a temporary blue-gray discoloration. Within twenty-four hours, the blue stain had entirely disappeared. A gray opalescent membrane was present until epithelization occurred, and the cornea, in each instance, was cloudy.

Since the reactions in most instances were severe and the discolorations variable and unpredictable, additional experiments were not performed using the metallic salts.

PRODUCTION AND TATTOOING OF EXPERIMENTAL CORNEAL SCARS

Corneal scars and pannus formation have been produced experimentally in a variety of ways. Ehlers[17] induced vascularization and scar formation in

the eyes of rabbits by repeated instillation of alcohol. Julianelle and Lamb[18] instilled or injected an antigen into the cornea of sensitized animals. Cogan[19] produced small discrete areas of scarring in rabbits by the local application of heat with the actual cautery and by the local injection of 0.1 normal hydrochloric acid or sodium hydroxide. Campbell and Michaelson[20] produced a "standard lesion" in the rabbit cornea by applying a platinum wire cautery of uniform temperature. Gifford and Steinberg[21] used herpes virus, smallpox vaccine, and trichloracetic acid to produce corneal scars in rabbits. Smallpox inoculations formed small, nonvascular scars. The herpes scars were unsatisfactory because of the severe prolonged reaction which ensued and which periodically flared up the latent herpetic process. Trichloracetic acid produced permanent scars when the undiluted solution was applied to the scarified cornea of the rabbits.

We have found that 10 per cent formalin, sodium hydroxide, or hydrochloric acid when applied to the intact cornea will produce moderately dense, white, permanent, nonvascular scars. When the corneal scars were mature, usually in three weeks, they were injected with various insoluble tattoo pigments, which, in turn, led to the injection of these same pigments into human corneal scars, when sufficient experience in mixing colors and skill in injecting the pigments had been gained by tattooing corneal scars in experimental animals.

The pigments* are insoluble, stable to heat and light, and essentially nonirritating when placed in the cornea or in the skin. The chemical composition and the color indices are: Black (Color Index 1311) is magnesium oxide. While this preparation is dark, it is not as black as "concentrated black" (Color Index 1308), which is lampblack. Blue (Color Index 1285) is cobaltous aluminate and is used for blending. Red (Color Index 1280) is mercuric sulfide. Orange (Color Index 1272) is cadmium sulfide. Yellow and brown (Color Index 1267) are natural ferric hydrates. For other shades of yellow and brown, one may use the ochers, the metallic oxides, which vary from light yellow to brown and red. The color is controlled by the amounts of hematite and limonite present. The artificial red ochers are produced by heating the natural yellow and brown ochers, thereby converting them to iron oxides.

THE TECHNIQUE OF TATTOOING CORNEAL SCARS

Preoperative Consideration: Anesthesia.—In adults, the operation may be performed with either local or general anesthesia. In children, however, general anesthesia is preferable. Holocaine, Pontocaine, and butacaine will produce a relatively quick local anesthesia without softening of the corneal epithelium, and without affecting the size of the pupil. While cocaine will produce satisfactory local anesthesia, it softens markedly the corneal epithelium and dilates the pupil.

Sodium pentothal will not cause any change in the size of the pupil during induction, unless there is a painful or exciting stimulus, in which event the

*The pigments were supplied by Fezandie and Sperle, Inc., 205 Fulton Street, New York City, N. Y.

pupil will dilate. When the second plane of the surgical stage of anesthesia is produced with pentothal, the pupils are slightly constricted. During this phase—which is the level of anesthesia for tattooing the cornea—very painful stimuli or anoxia will cause some dilation of the pupil.

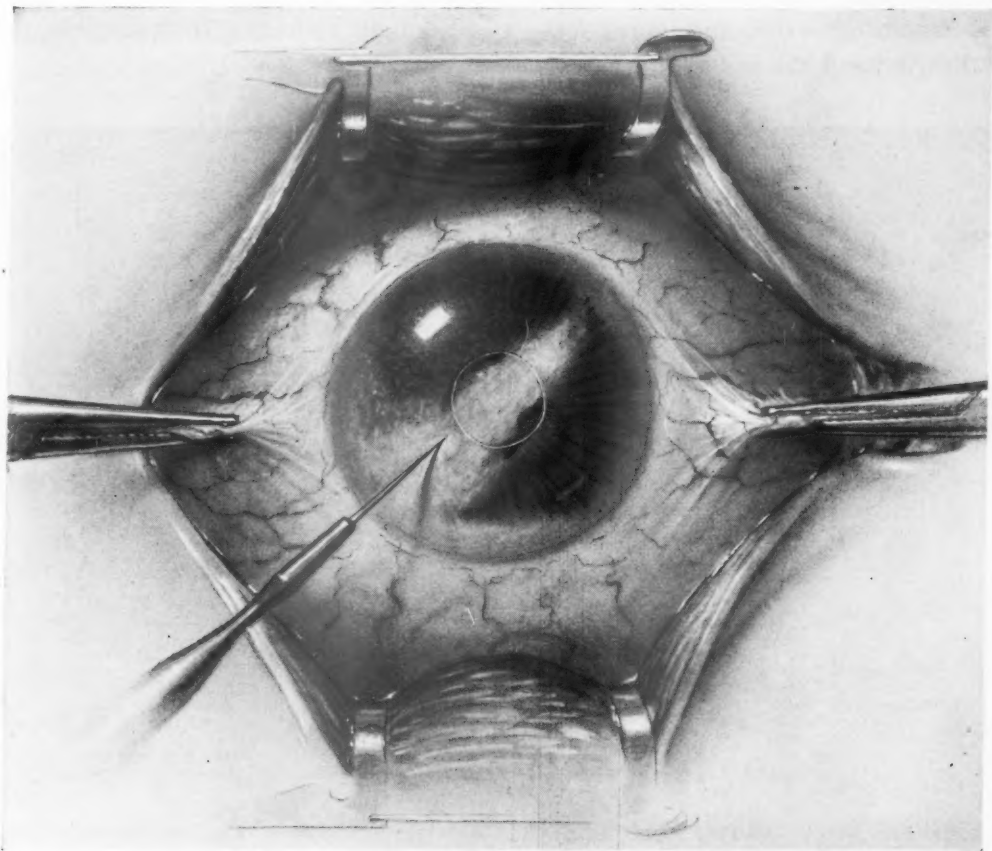

Fig. 2.—Corneal scars, congenital and posttraumatic defects of the pupil and cornea are of infinite variety, form, and contour. Since eyes possess many colors, shades, and tones, a general outline which is applicable to most cases is presented.

A speculum is inserted on each side to visualize both eyes simultaneously. The eye to be operated upon is immobilized with grasping forceps or clamps which are placed about midway between the limbus and canthus. These are not released until the termination of the procedure. Meticulous care should be exercised in outlining the periphery of the cornea. Implantation of pigment should begin at the limbus, proceeding toward the pupil in a radial direction to obtain the effect of striation. The color of the pigment should be slightly darker than the normal iris tone.

A corneal trephine or a cutaneous punch is used to define the periphery of the pupil. This pupillary trough is made by rotating the instrument in a to-and-fro motion. Into this circumscribed area, concentrated black pigment is injected to assimilate the pupil.

During induction of anesthesia with ether, there is some dilatation of the pupils because of the liberation of adrenalin. During the second plane of surgical anesthesia with ether, the pupils are essentially normal. Painful stimuli will produce little, if any, effect on the pupillary size because it blocks the afferent limb of the reflex arc. In the third plane of surgical anesthesia, dilation of the pupils occurs because the pupillary muscles are paralyzed.

Preoperative Plan: Size of Pupil and Iris.—The size of the pupil should be that of the normal pupillary opening under ordinary lighting conditions.

A diameter of 4 mm. is a pleasing size. The pupil size should be determined prior to operation, since the anesthetic agent or the intense illumination of the operating room will cause variability in the pupillary size. The size of the iris is determined by careful measurement with dividers as compared with the normal eye.

Operation.—The instruments are sterilized by boiling. The pigments are autoclaved and stored in stoppered Wassermann tubes.

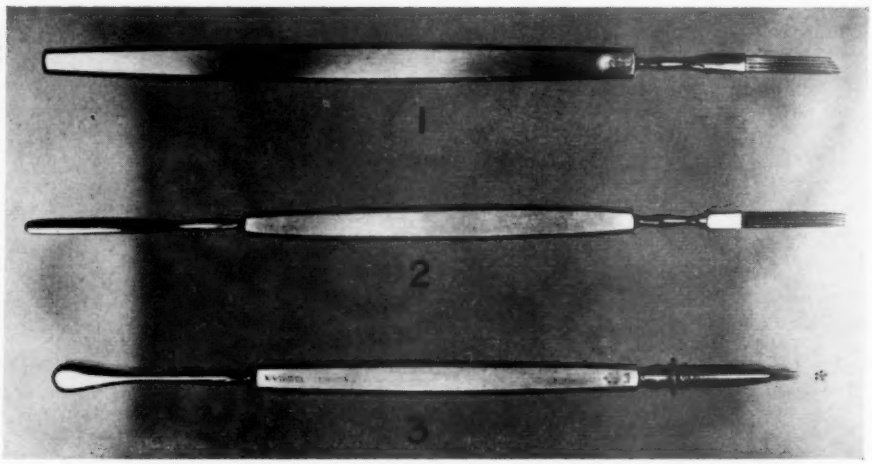

Fig. 3.—The special tattoo needles were supplied by the Edward Weck Company, Brooklyn, N. Y. Because of their delicate temper, they should not be boiled. Needle No. 1 is invaluable for defining the limbus and the pupillary margin. It should be inserted into the cornea, as shown, with the longest needle down. The remaining needles in the echelon will serve as a guard to avoid penetrating the anterior chamber. When sufficient experience has been gained and the "feel" of tattooing the cornea acquired, one will find needles No. 2 and No. 3 very helpful to insert the iris tone, shading, and color details, and to assimilate the normal striation.

The needles are invaluable when implanting pigment into eyebrows, eyelashes, lips, and into free grafts and flaps, and when attempting to conceal scars and other disfigurements.

First Stage.—After satisfactory anesthesia has been obtained, a speculum is inserted into each orbit to visualize both eyes simultaneously. The eye to be tattooed is immobilized with mosquito clamps or lock forceps which grasp the conjunctiva at three and nine o'clock (Fig. 2). They are placed about midway between the limbus and each canthus. In this manner, the eye is immobilized effectively in any desired position. Since the clamps may cause tiny perforations or serrations in the conjunctiva, they are not released until the termination of the operation in order to prevent the possibility of pigment entering the clear areas of the conjunctiva.

The size of the pupil and iris, which was determined previously, is now rechecked by careful measurement, with dividers, of these structures on the normal side. The basic color of the iris is obtained by mixing several dry pigments in a porcelain palette and adding saline solution until the consistency of a thin paste is obtained. A small amount of mixed pigment is then spread thinly on the gloved finger and compared with the color of the iris on the normal side. This basic color should be slightly darker than the normal iris. Then using a No. 1 or No. 2 tattoo needle (Fig. 3), the periphery of the cornea

or limbus to be tattooed is outlined with the basic color pigment. Meticulous care should be exercised in defining this border. The implantation of pigment should begin at the limbus, working toward the center of the eye in a radial direction. The operator may find it advantageous to change his position occasionally from the sides to the head end of the table, rather than to rotate the eye. The injection of the pigment from the periphery to the center will assimilate quite accurately the normal striation of the iris (Figs. 2, 4, and 5).

Fig. 4.—A 21-year-old man was struck by a flying stone at 10 years of age, which resulted in the loss of serviceable vision in the left eye. A dense posttrauma opacity of the iris and lens detracted markedly from the patient's otherwise pleasing appearance. Ophthalmologic consultants advised tattooing the cornea since there was marked destruction of the retina as the result of the injury, and hence, no chance of restoring vision.

Insoluble pigment was tattooed into the cornea on two occasions, followed by a squint operation to correct the exotropia. Postoperative photographs taken more than one year later disclose no fading, dispersion, or diffusion of the pigment. The camouflage has been so effective that the patient has passed successfully several "rigid" medical examinations. The color of the normal iris was a fluorescent blue-green, a rather difficult tone to match with insoluble pigments.

It is important to insert the needle at any angle of 45 to 60 degrees (Figs. 1 and 2) so that a line of pigment rather than a tiny spot in or beneath the epithelium will be produced. Iris color tone is then added using a No. 3 tattoo needle (Fig. 3) in a radial fashion until the scarred area is quite homogeneous in color. Any pigment which encroaches upon the pupillary area will subsequently be covered by black. Care should be taken to avoid entering the anterior chamber. The cornea will tolerate a rather surprising amount of trauma and one need not cease injection of the pigment until the cornea is quite "chewed up," unless one is tattooing a conical cornea, in which case one

should proceed with caution, to avoid entering the anterior chamber with possible resultant collapse of the globe. The eye is flushed frequently with saline solution then wiped dry very gently with wisps of cotton or applicators. Any visible areas of scarring are then tattooed until the iris color is quite homogeneous.

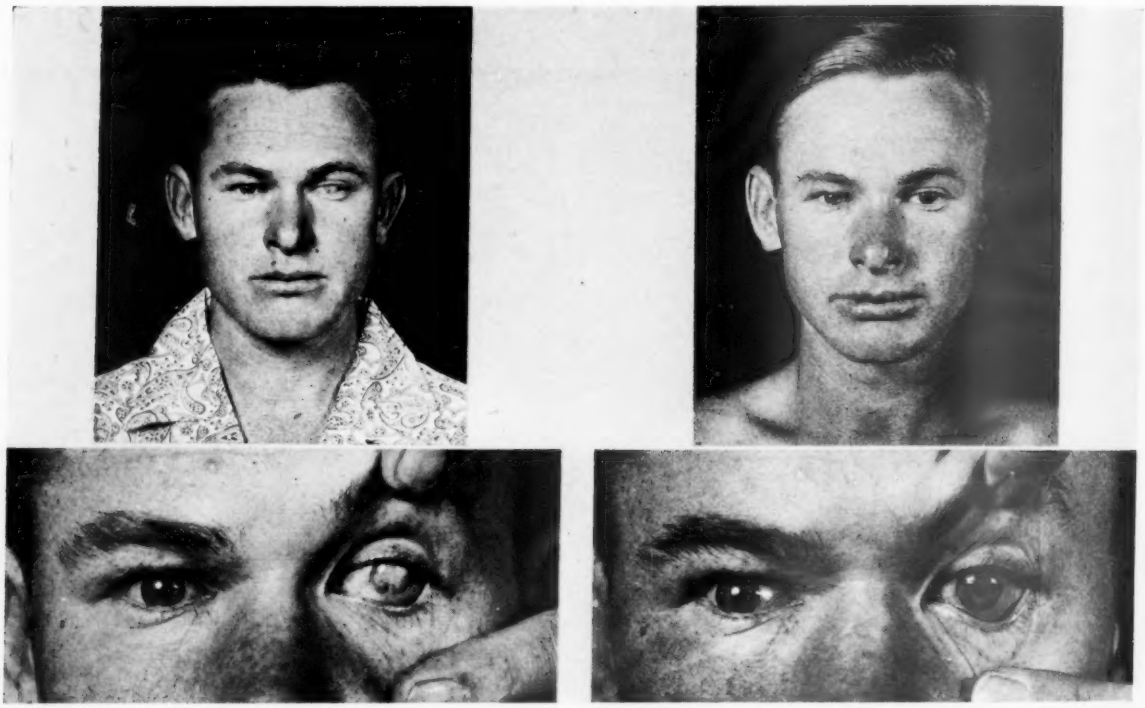

Fig. 5.—A 22-year-old man received a penetrating wound of the left eye at 13 years of age when a jagged piece of wood from a chopping block pierced the globe. An operation is said to have been performed immediately to remove the foreign body. However, an infection developed which resulted in dense scarring of the cornea and complete loss of vision in the injured eye. In many penetrating wounds of the eye, the internal arrangement is disrupted so that the lens is pushed backward into the posterior chamber. With concomitant hemorrhage and/or infection, the function of the retina is impaired or destroyed completely.

This dense corneal scar was tattooed on three occasions, approximately ten days apart. On each occasion the patient remained in the hospital only forty-eight hours.

The color of the normal iris was a blue-gray. Photographs disclose the appearance of the eyes more than one year later.

The pupil is inserted in the following manner: Using a Keyes cutaneous punch or a corneal trephine, of the size corresponding to that of the predetermined pupillary measurement, a circular incision is made in the cornea to define the limits and the periphery of the pupil. This corneal trough is made by rotating the instrument in a to-and-fro motion. Care and caution are exercised to avoid incising the cornea deeper than about one millimeter. Into this circumscribed area (Fig. 2), concentrated black pigment is injected. The appearance of the eye to this point will seem to lack luster. However, after the pupil has been inserted, a very pleasing appearance results, which should resemble that of the normal eye. Definite brilliance and sparkle are obtained by inserting flecks of orange, yellow, blue, green, or brown.

While we always attempt to complete the tattooing in a single operation, we have never been able to accomplish this end unless the scar was small or involved only part of the iris. The eye is flushed with saline solution using a bulb or ear syringe to wash away all excess pigment. The eye is wiped dry with cotton wisps, following which petrolatum or penicillin ophthalmic ointment is placed in the eye before the clamps and speculum are released. The eye which has been tattooed, and sometimes both eyes, are covered with a small gauze dressing.

Fig. 6.—A penetrating wound of the right eye received during early childhood resulted in loss of serviceable vision in the injured eye. During grammar school, the patient was the recipient of unkind remarks by her classmates. During high school and college she became increasingly conscious of her deformity. Because the eye was blind, she was not an acceptable candidate for a transplant operation. Prosthetic shells could not be worn because of constant discomfort and uncontrollable lacrimation which persisted for more than twenty-four hours after the shell was removed.

A dense scar covered almost all of the corneal area. Its surface was irregular, conical in outline, and contained calcareous deposits. There was an exotropia of about 10 degrees.

Insoluble pigment was tattooed into the scarred cornea in May, 1946, and again in February, 1947, to match accurately the brown iris of the normal eye. Postoperative photographs disclose the appearance of the patient more than three years later. The exotropia has not been corrected.

Postoperative Phase.—Following operation, patients may experience varying degrees of photophobia. If this is pronounced, they are placed in a darkened room. Dark sun glasses will frequently bring relief. Pain is not pronounced. We have never instilled a local anesthetic agent into the eye following operation. Although there is some injection of the eye for about one week, discomfort is usually not present after the first or second day. About one-half of our patients are discharged from the hospital on the second or third

postoperative day to be followed on an ambulatory basis for about one week or ten days when the eye is ready for the next stage of the injection of pigment.

Second Stage.—Although an attempt is always made to complete the tattooing and to make the iris and pupil homogeneous at the first sitting, this is possible only when the scar is small. A second stage, therefore, is not due to fading, but rather, to an insufficient number of minute injections made at

Fig. 7.—A 38-year-old woman received a screw driver penetrating wound of the right eye approximately five years ago. Definitive treatment was received elsewhere. The ophthalmologic surgeon is said to have sutured the tears of the cornea and sclera. The patient was hospitalized for about one month. A posttraumatic cataract was removed about three years following the injury.

A corneal scar, such as here represented, which involves part of the iris and the pupillary area, may give rise to diffusion of light within the eye. The scar may thus act as a frosted glass in front of the normal eye. In the place of the normal refraction of the light rays on the macula of the retina, there is widespread dispersion of the rays at all angles. This phenomenon produces blurred images and diminishes visual acuity.

Tattooing of the cornea on a single occasion produced a pleasing result from the cosmetic standpoint. In addition, vision was enhanced since the opacity was converted from one which transmitted dispersing pencils of light throughout the eye to one which absorbs the light rays. By tattooing a central corneal opacity encroaching upon the pupillary area, but not completely occluding it, one creates a condition comparable to a contracted pupil. Increased light results, since some of the annoying peripheral rays are obstructed.

the first operation. In the second operation, additional iris and pupil tone are added, so that no areas remain which do not contain pigment. If the operator is satisfied that the basic iris color is well matched with the opposite eye and that there are no areas of untattooed scar visible, the iris is flecked with orange, yellow, blue, green, red, or brown to match accurately the sparkle colors of the normal eye. The limbus or the periphery of the iris is a diffused,

circular, blue-gray line (Fig. 2). This effect may be produced by tattooing the periphery with blue pigment to which black has been added. In many instances, a light zone of pigmentation surrounds the pupillary area. This effect can be achieved by injecting the rim of the pupil with a light pigment.

Only rarely is a third or fourth tattooing necessary. If a touch-up procedure is required to perfect the camouflage and to make both eyes objectively the same, a period of four to six weeks should elapse following the last procedure whether the previous operation was a tattooing or muscle imbalance operation.

DISCUSSION

It is true that many individuals quite readily compensate for physical or physiologic impairments. However, in the case of ocular disfigurement, there is essentially no mechanism that will shield a defensive individual from a continued attack upon his self-esteem, for his inner security is assailed each time he looks into a mirror. These unfortunates, children or adults, should, therefore, be given an opportunity to have this barrier removed, even though vision cannot be restored and life is not endangered by the affliction. They should not be encouraged to endure the misery and abuse to which they are predestined, for no one knows the indelible mental effects produced on the afflicted. The need for plastic or ophthalmologic surgery for the correction of the deformity and the elimination of the handicap and the possible mental sequelae is, therefore, evident. To many physicians, however, the eye may be a rather uninteresting part of the body, unless there is some serviceable vision. To the individual, however, a corneal scar may be the primary object of his concern, though no vision exists, for to him and to everyone else the eyes are the windows of his soul, and this regardless of whether the deformity is congenital or the result of injury or disease.

Because substitute measures such as prosthetic shells had failed to conceal the deformity or could not be tolerated, tattooing the corneal with insoluble pigments was conceived by one of us (K. P.) more than six years ago. The procedure has been uniformly successful and entirely free of complications. House officers perform the operation with skill and dexterity. It is advisable, however, to have an artist mix the various pigments at the time of operation and to be able to vary the tone of the iris pigment as is required in each instance. Brown eyes are easy to tattoo and to match the color. Eyes that are gray, blue, or green (Figs. 4 and 5) require more skill to match accurately the color and brilliancy tones of the normal eye.

Most eye surgeons agree that an individual basically blind from a complete corneal opacity, whether superficial or deep, is entitled to the benefit of a corneal graft. And as a result, keratoplasty has attracted much popular interest. Many blind or partially blind persons have sought a transplant operation in the hope that their sight could be restored. Many, however, have been disappointed because numerous instances of blindness are due to causes other than opaque cornea. Among the types of corneal opacities covering the pupillary area, some are susceptible to treatment by corneal transplantation,

which gives the best results as far as improvement of vision is concerned. Other opacities are unfavorable for keratoplasty because of excessive density of the scar or pronounced superficial vascularization, which would render the transplant nebulous or opaque.

A corneal leukoma or macula over the pupillary area may give rise to diffusion of light within the eye. The scar may thus act as a frosted glass in front of the normal eye. In the place of the normal refraction of the light rays on the macula of the retina, there is widespread dispersion of the rays at all angles. This phenomenon produces blurred images and diminished visual acuity. This reduced vision varies with the density of the scar. By converting the opacity from one which transmits dispersing pencils of light throughout the eyeball, to one which absorbs the light rays, the disturbing element in the production of good vision is eliminated. By tattooing a central corneal opacity encroaching upon the pupillary area, but not completely occluding it, one creates a condition comparable to a contracted pupil. Increased light may result, since some of the annoying peripheral rays are obstructed. Instead of developing spherical aberration, with consequent reduced visual acuity, these rays are absorbed.

CONCLUSIONS

Even though an eye may be blind, tattooing will conceal a conspicuous deformity which may have been most harassing and the cause of somatic and psychic disturbances.

Tattooing may improve visual acuity by reducing the area of an abnormal cornea through which dispersing pencils of light pass. The tattooed area will absorb the annoying peripheral rays.

Attempts to stain the normal or scarred cornea of experimental animals with metallic salts were unsuccessful.

A method of permanent pigment injection of corneal scars is described which has been used more than seventy-five times and without complication. Patients with congenital corneal opacities, posttraumatic corneal scars, postoperative conjunctival flaps, operative defects of the iris, heterochromia, polychromia, and congenital colobomas have been tattooed with results that have been pleasing to us and gratifying to our patients.

Since there are no lymphatics in the cornea, there is little, if any, diffusion, dispersion, or change in the color of the pigments implanted in the cornea. Some of our patients have been followed for more than six years without change in the color or size of the pupil or iris.

A prosthetic shell is not tolerated by patients with corneal scars in which there is calcareous deposit. When a prosthesis is tolerated, it is quite readily recognized; movements of the eyes may not be simultaneous and of the same degree; because of the change in orbital volume, the palpebral fissures may not be symmetrical. Tattooing eliminates these abnormalities and the care of a prosthetic appliance.

Acknowledgement.—We are indebted to Mr. Elon Clark and Mr. Robert Blake of the Department of Medical Illustration for their assistance in preparing and mixing the pigments and for their advice in formulating the plan and the execution of the corneal tattooing in each of our patients.

We are deeply grateful to Dr. Banks Anderson, Professor of Ophthalmology, for his guidance in pre- and postoperatively evaluating our patients who have had the eye tattooed to conceal congenital or operative defects of the iris, polychromia, heterochromia, corneal scars, conjunctival flaps, and so on. Dr. Anderson and his associates have performed operations to correct muscle imbalance and squints on some of our patients.

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PHEOCHROMOCYTOMA

The Use of Adrenergic Blocking Agents in the Operative Management

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THE operative mortality reported for pheochromocytoma varies from 15 to 37 per cent.[1] The course during operation is characterized by two phases, one of extreme hypertension followed by one of prolonged hypotension. During the first phase there are alarming fluctuations in blood pressure and cardiac rate with periods when blood pressure and pulse cannot be obtained alternating with periods of extreme hypertension. During the second phase the degree of hypotension may resemble vasomotor collapse. Death may occur during either phase.

In the past, vasodilators such as amyl nitrite have been used with little success during the hypertensive phase. Most attention, however, has been directed to the secondary hypotensive phase. Since this occurs at about the time that the tumor is removed, the hypotension has usually been attributed to its removal, and epinephrine or other vasoconstrictors have been used as replacement therapy.

In three patients with proved pheochromocytoma studies were made on induced hypertensive attacks and their control with adrenergic blocking agents. In one patient Priscoline (2-benzyl-4, 5 imidazoline hydrochloride) was used to control the usual cardiovascular complications during excision of the tumor. In another, Dibenamine* (dibenzyl beta chlorethyl amino hydrochloride) was used during the performance of a prefrontal lobotomy for intractable pain. The results throw some light on the mechanisms responsible for the cardiovascular dysfunction and suggest a more rational form of therapy.

MATERIAL

Case 1.—This patient was a 39-year-old female who was studied only preoperatively. This case is to be reported elsewhere.[2]

Case 2.—This patient, a 37-year-old man, was admitted to the New York Hospital complaining of five years of intermittent attacks characterized by blanching of the skin, palpitations in the epigastrium and chest, generalized weakness, tremor of the hands, profuse sweating, and generalized headache. The attacks lasted from three to fifteen minutes and occurred at least once daily, occasionally four to five times per day. They were sometimes precipitated by bending, by exercising, and by taking a shower.

Temperature, pulse, and respiration were normal, and the general physical examination was unremarkable. The blood pressure ranged from 120/80 to 140/100 with occasional read-

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*Dibenamine was supplied by Givaudan-Delwanna Inc., and by the Smith, Kline & French Laboratories, Philadelphia, Pa.

ings of 160/110. On three occasions when the blood pressure was measured during spontaneous attacks, it was 200/160.

In the laboratory findings, repeated urinalyses done before and after attacks were unremarkable, as was the blood sugar. The blood count, blood urea nitrogen, glucose tolerance test, phenosulfonephthalein excretion, and urine concentration and dilution tests were all within normal limits. A cold pressor test did not show significant change in blood pressure. The electrocardiogram was unremarkable as were the lung fields and configuration of the heart on roentgenogram. An intravenous pyelogram showed a circular, ill-defined shadow over the upper pole of the left kidney with downward displacement of the kidney.

CASE 3.—This 25-year-old woman had had a pheochromocytoma of the right adrenal gland removed seven and one-half years, and another of the left adrenal gland removed three and one-half years prior to admission to the New York Hospital. One and one-half years after the second operation typical attacks characterized by blanching of the skin, palpitation, and precordial pain recurred. These occurred spontaneously and could easily be precipitated by histamine (.025 mg. intravenously) following which the blood pressure rose from 130/80 to 260/180. X-ray examinations of the chest revealed multiple areas of nodular density in both lung fields, and a nodule in the neck on biopsy proved to be metastatic malignant pheochromocytoma. Because of the intractable pain in the chest and lower extremities it became necessary to perform a prefrontal lobotomy in this patient.

ATTACKS PRECIPITATED BY DRUGS

Special studies were made using histamine (0.025 to 0.050 mg. intravenously), tetraethylammonium (TEA*) (100 to 500 mg. intravenously), and nitroglycerine (0.30 to 1.20 mg. sublingually). Each of these drugs was used to precipitate typical hypertensive attacks but none was consistently successful and therefore not completely reliable or specific as a diagnostic agent. Any drug which produces a fall in blood pressure may be used since the precipitation of an attack appears to depend on this property, which is the only one common to all drugs used.

In contrast to the characteristic changes which occur during spontaneous attacks or those produced by other drugs, TEA in adequate dosage precipitated in both patients a series of severe attacks with marked cardiovascular dysfunction resembling the changes which occur during operation. The features of the attacks precipitated by histamine and TEA are shown in Figs. 1, *a* and *b* and 2, *a* and *b*.

Attacks occurring spontaneously or produced by drugs other than TEA are characterized by slowing of the pulse as the blood pressure rises. Irregularities in rhythm are slight and ventricular premature contractions occur only occasionally. The blood pressure curve is usually monophasic and the pressure returns to the original level. Occasionally, there may be two or three similar attacks in rapid succession.

When TEA, 200 mg. intravenously, was administered to one patient (Case 2), it precipitated a series of severe attacks of alternating hypertension and hypotension which persisted for fifty-five minutes, followed by a prolonged period of hypotension. The patient complained of precordial pain throughout the attack and for eight to ten hours after. Electrocardiograms done one to two

*TEA was supplied as Etamon by Parke, Davis & Co., Detroit, Mich.

hours and twenty-four hours after the attacks showed no significant changes. Between the hypertensive attacks there were periods when the radial pulse was absent and the blood pressure could not be obtained by sphygomanometer. The similarity between this sequence of events and that which usually occurs at operation is impressive.

In contrast to the bradycardia and slight arrhythmia usually noted during a spontaneous attack or one produced by other drugs, TEA produced tachycardia (with rates in excess of 200 per min.) and marked ventricular arrhythmia. Although the record (Fig. 2, *b*) is not standardized and the paper

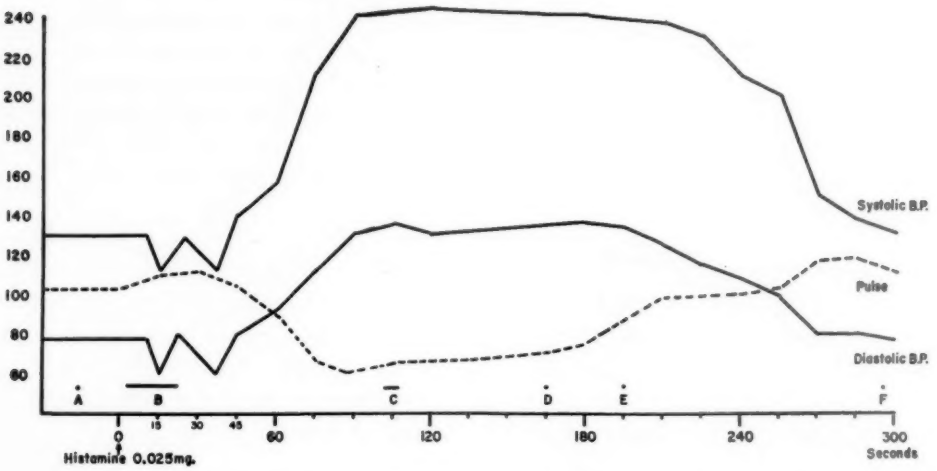

Fig. 1, *a*.—Changes in blood pressure and pulse during a typical attack precipitated by histamine. *A*, *B*, *C*, *D*, *E*, and *F* refer to the points from which the segments of the continuous record (Fig. 1, *b*) are taken.

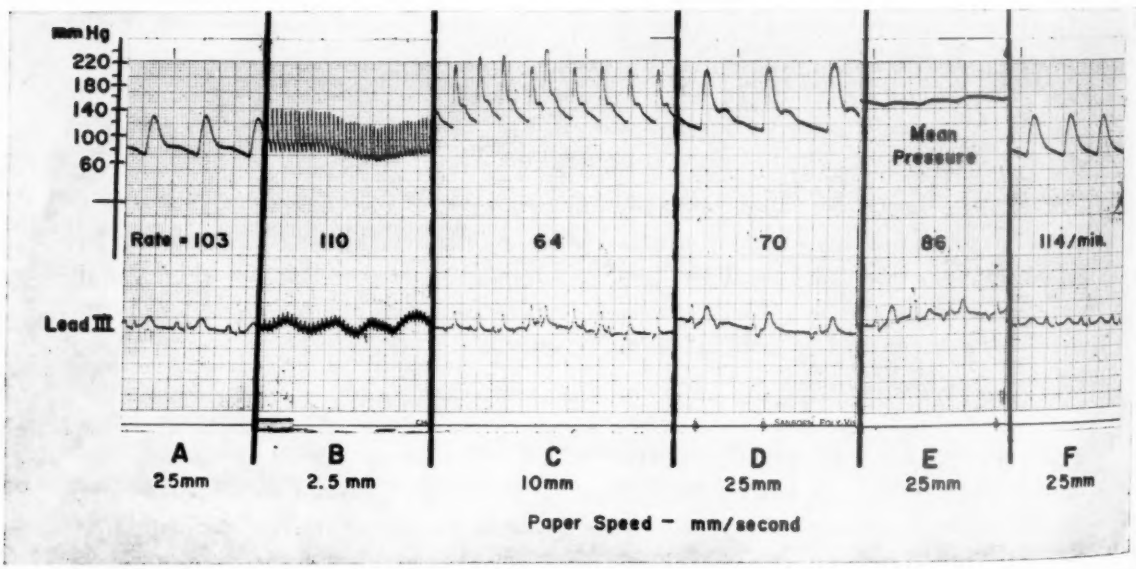

Fig. 1, *b*.—Segments of continuous simultaneous records of the electrocardiogram (Lead III) and intra-arterial (femoral) blood pressure taken during the attack shown in Fig. 1, *a*.

speed is slower than the usual speed of the electrocardiogram, definite bursts of ventricular tachycardia are recognizable. These correspond with the periods of marked fall in blood pressure.

The augmentation of the effects of pressor drugs by TEA has been reported by Page[3] and Hoobler, Moe, and Lyons,[4] who attribute it to the block-

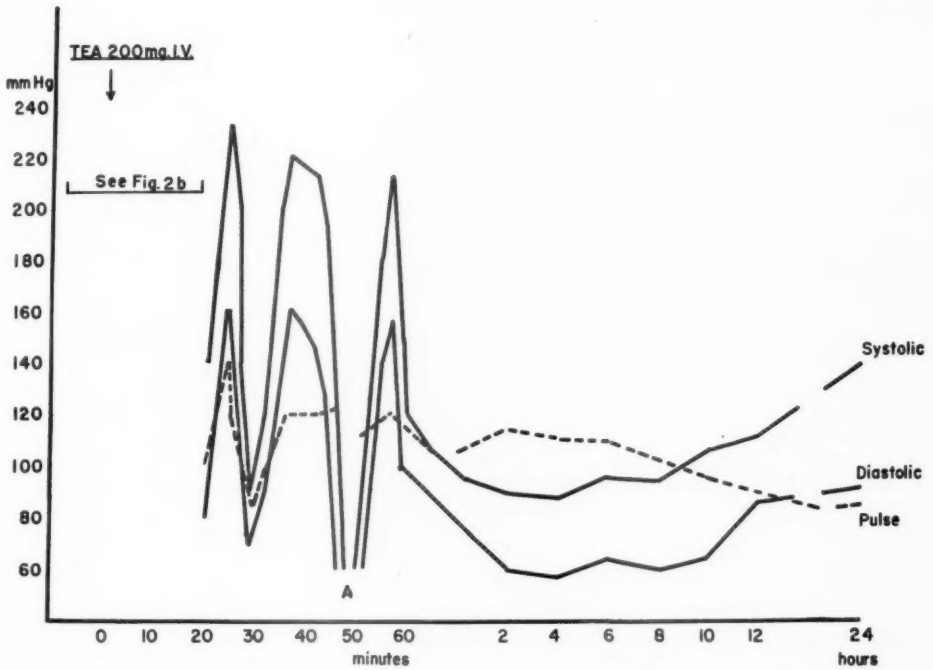

Fig. 2, *a*.—Changes in blood pressure and pulse during the last three of five attacks precipitated by TEA. Blood pressures are brachial, measured with a sphygomanometer. At *A* no pulse or blood pressure was obtainable. Direct recordings during the first two attacks (0 to 20 minutes) are shown in Fig. 2, b.

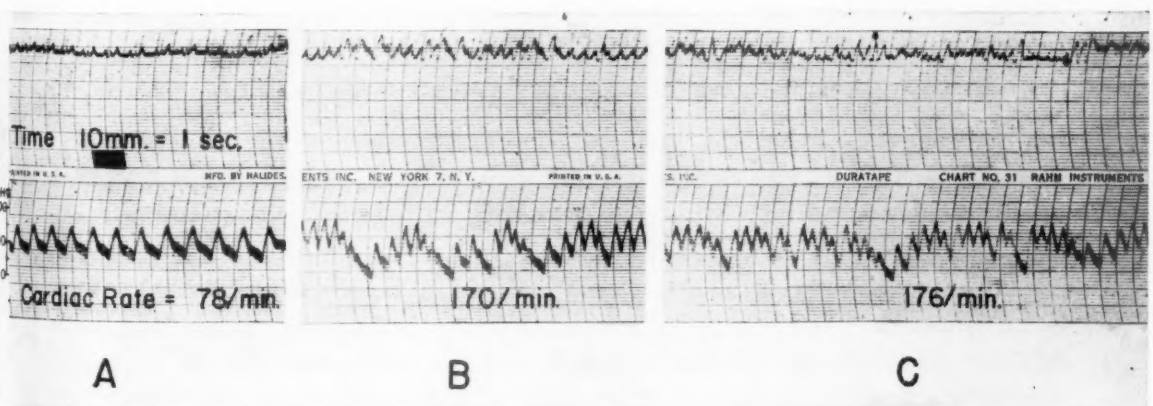

Fig. 2, *b*.—Segments of continuous simultaneous records of the electrocardiogram (Lead III) and intra-arterial (femoral) blood pressure during attacks precipitated by TEA. *A*, before TEA; *B* and *C*, during attack. The intra-arterial tracing was made with an alternating current amplifier and therefore does not show absolute values for slow or sustained changes which exceed the four-second degeneration period of the system.

ing of autonomic compensatory responses which normally buffer a rise in blood pressure. Certainly the tachycardia which occurs instead of the usual bradycardia suggests that at least the compensatory buffering mechanism for the control of cardiac rate has been blocked. Whether the extreme response to TEA is due entirely to this blocking action or to the secretion of larger amounts of circulating epinephrine is not yet clear but additional studies now in progress may clarify this point.

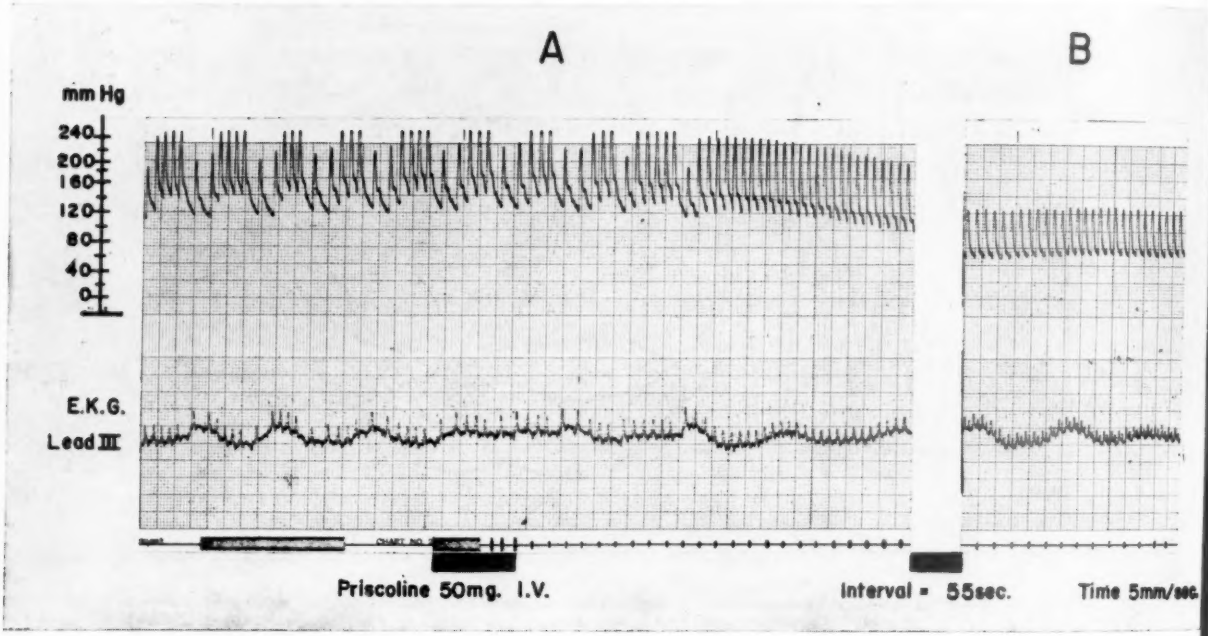

Fig. 3.—The effect of Priscoline on the blood pressure (direct femoral) and the electrocardiogram (Lead III) administered fifteen seconds after the onset of an induced attack. *A*, return to regular rhythm and beginning fall in blood pressure ten seconds after Priscoline. *B*, return to normal sixty-five seconds after Priscoline.

THE CONTROL OF HYPERTENSIVE ATTACKS BY ADRENERGIC BLOCKING AGENTS

Dibenamine, Priscoline, and 933F or "benzodioxane" (piperidyl-methyl benzodioxane) were each used to prevent or to terminate attacks which occurred spontaneously or were precipitated by drugs. The preoperative studies made on Case 1 are to be reported elsewhere.[2] In Case 2, Priscoline was used and found capable of rapidly terminating induced attacks. Clinically the effects were dramatic. Within a period of seconds after the intravenous administration of Priscoline (50 mg.) during an attack, the hands and face flushed, the severe headache subsided almost instantaneously, and precordial pain and palpitation rapidly disappeared. The effect on the blood pressure is shown in Fig. 3. It is noteworthy that on its return the blood pressure does not fall below the original normal level indicating that epinephrine reversal does not occur.

In Case 3 the effect of intravenous epinephrine after the administration of Dibenamine was studied. Prior to Dibenamine a definite pressor response was obtained with 0.01 to 0.02 mg. of epinephrine intravenously, the blood pressure rising from 120/80 to 150/110. Six hours after the administration of Dibenamine (7.5 mg. per kilogram) 0.04 mg. epinephrine caused only vasodepression, the blood pressure falling from 120/80 to 90/60. A pressor response equivalent to that observed before Dibenamine required approximately ten times as much epinephrine (0.1 mg.).

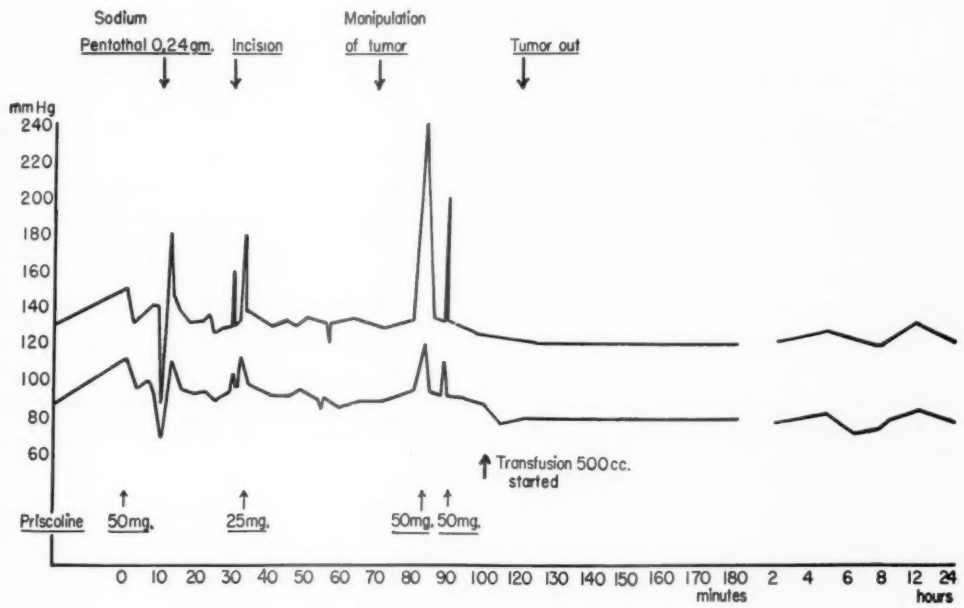

Fig. 4.—Course of the blood pressure during operation and postoperative period in Case 2. Blood pressures prior to the incision and postoperative are brachial measured with a sphygomanometer. Blood pressures from the time of the incision to the termination of the operation (180 minutes) are taken from the continuous record of intra-arterial (dorsalis pedis) pressure. Changes in pulse were unremarkable and paralleled the changes in blood pressure.

OPERATIONS

Case 2.—On Aug. 18, 1949, one week after the patient was admitted to the hospital, an encapsulated pheochromocytoma weighing 99.5 Gm. was removed. A left flank exposure with resection of the twelfth rib and detachment of the diaphragm was used. The anesthesia was induced by sodium pentothal and maintained by intratracheal ether and oxygen. The right dorsalis pedis artery was cannulated and a continuous record of intra-arterial pressure was made using an electromanometer (Sanborn). Fig. 4 illustrates the course of the blood pressure during operation.

Among the more important features of the course, the response to sodium pentothal is noteworthy. This drug was used deliberately although it is known to precipitate severe attacks. A preliminary dose of Priscoline (50 mg.) was given prior to induction with the expectation that it would counteract the effects of sodium pentothal. It was felt that changes in blood pressure would furnish an index of the adequacy of the dosage of Priscoline. In spite of the profound fall in blood pressure which resulted from the sodium pentothal, there

was only a slight transient rise in blood pressure thereafter. After the first spike of hypertension which occurred during manipulation of the tumor, the time required for blood pressure to return to normal was four minutes. This was considerably longer than had been observed with induced attacks and was probably due to inadequate dosage of Priscoline. The second spike of hypertension began shortly after the first, and the second dose of Priscoline (50 mg.) was given immediately. The rapid response is similar to that observed preoperatively. Most important is the complete absence of the secondary phase of hypotension. Save for the fall of blood pressure produced by the sodium pentothal induction, the blood pressure never fell below 110 systolic and 70 diastolic. After removal of the tumor the blood pressure leveled off at 120/80 and remained between that level and 140/90 throughout the entire postoperative course in the hospital.

A total of 175 mg. of Priscoline, 500 c.c. of citrated blood, and 1,000 c.c. of 5 per cent glucose in distilled water were given during the operation. After each dose of Priscoline salivation and bronchial secretions increased but were easily managed by suction. No other untoward effects were noted. The tumor was assayed* and found to contain 0.8 mg. of active pressor substances per gram of tumor.

CASE 3.—A prefrontal lobotomy was performed on Jan. 19, 1950. Dibenamine (6.0 mg. per kilogram) was administered two hours prior to operation. Anesthesia was induced with sodium pentothal and maintained with intratracheal ether and oxygen. Following the injection of sodium pentothal the blood pressure fell from 110/80 to 70/50. This was followed only by a gradual rise to the original level. Save for the fall due to the sodium pentothal the blood pressure remained between 100/70 and 120/80 throughout the entire procedure.

Comment.—It has been observed that exploratory operations in which the tumor is not discovered, and unrelated operations on patients with pheochromocytoma, are frequently attended by profound cardiovascular dysfunction. A prolonged period of hypotension may occur during any operation on these patients. At least one case has been reported[5] in which a prolonged period of hypotension beginning during operation resulted in death five hours later even though the tumor was not removed. Yet the marked fall in blood pressure which occurs during removal of these tumors has been attributed to withdrawal of "excess pressor substances."[6]

It has been demonstrated that a prolonged fall in blood pressure occurred after a series of severe uncontrolled hypertensive attacks were precipitated by TEA. In the same patient, when Priscoline was used to control hypertension during the operation, the hypotensive phase did not occur after removal of the tumor. This more than anything else refutes the claims of those who maintain that the hypotension results from removal of the tumor and that replacement therapy with epinephrine or other vasoconstrictors is indicated. That some relationship exists between the hypertensive and hypotensive phases appears obvious. The serious ventricular arrhythmia observed during induced attacks suggests that it is the result of epinephrine intoxication. This pharmacologic action of epinephrine is well known.[7] The toxic effect may be due to the high concentration of epinephrine alone or to its augmentation by TEA in induced attacks or by anesthesia during operation. Although the exact mechanism

*By Dr. Harry Gold.

is not clear at present it appears that the phase of hypotension is cardiac in origin. If this is true, the administration of epinephrine is difficult to justify. It seems preferable to prevent the hypertensive attacks and for this purpose the adrenergic blocking drugs provide a potent means.

Snyder and Vick[8] reported the use of 933F during operation in one patient without success but it is probable that it was used too late. During the preparation of this report Grimson, Longino, Kernodle, and O'Rear[9] reported the successful use of another adrenergic blocking agent 2(N, para-tolyl-N (m hydroxyphenol) amino methyl) imidazoline hydrochloride in one patient. Dibenamine was used preoperatively by Spear and Griswold,[10] but there are no reports of its use during operation.

An ideal adrenergic blocking agent is not yet available. Of those in common use Dibenamine is by far the best with respect to specificity, effectiveness, and duration of action. In addition, it possesses the peculiar property of producing a "nonequilibrium" blockade, or a blockade which remains effective in spite of any increase in the concentration of epinephrine. This is in contrast to the imidazolines and benzodioxanes whose blockade can be broken through by increasing the concentration of epinephrine. The imidazolines, on the other hand, have the advantage of rapid action in contrast to Dibenamine which requires one hour or more to produce an adequate blockade.

Since pheochromocytomas vary in their activity, it is not possible to predict the concentration of epinephrine with which one may have to deal during operation. A dose of Priscoline which is effective in one case may therefore be inadequate in another, and in some the side actions of the drug may prohibit the administration of a dose sufficient to prevent hypertension and cardiac arrhythmia. Theoretically, Dibenamine has none of these disadvantages since a complete blockade, once produced, cannot be broken through by any increases in epinephrine. In Dibenaminized animals even 10 mg. per kilogram of epinephrine causes only vasodepression and up to five hundred times the standard dose of epinephrine fails to produce a significant arrhythmia under cyclopropane anesthesia.[11] The dosage of Dibenamine in animals, however, is two to three times that ordinarily used in man. The smaller dosage ordinarily used in man does not produce a complete blockade and will undoubtedly give adequate protection only in some cases of pheochromocytoma. Whether the usual dose can be increased to the point of complete blockade without danger must yet be determined. Further studies along these lines are being made. Perhaps a more effective agent will become available in the future. At this time it is safe to conclude that the use of adrenergic blocking agents is of definite value in the prevention of the usual cardiovascular complications which occur during operations for pheochromocytoma. Of the drugs now available, Dibenamine is the agent of choice. In those cases in which a pheochromocytoma is discovered during the course of another operation and there is not sufficient time for administration of Dibenamine, the imidazolines have been advantage of rapid action. The method has a rational basis and is worthy of further trial.

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DISCUSSION

DR. GRIMSON.—It is certainly a pleasure to congratulate Dr. Console, Dr. Dunbar, and Dr. Ray on their excellent and courageous studies. I know what they went through because after four years of study of adrenolytic drugs and of waiting for an appropriate patient we also encountered a patient with pheochromocytoma and undertook treatment. There was serious worry concerning the hypotension that follows removal of adrenalin-secreting tumors. Until now it had not been determined whether this hypotension resulted from deprivation of adrenalin or was collapse following adrenalin intoxication and paroxysmal hypertension. Therefore, the administration of adrenolytic drugs as they did it and as we did it could have caused troublesome hypotension or shock.

We have, however, since our first report, had a chance to use an adrenolytic drug C-7337 in three patients before and during operation for pheochromocytoma with successful outcome. In each of the three preliminary hypertension was avoided and vasomotor collapse with the drug or following removal of the tumor did not occur. Postoperative support for hypotension was not needed. It is our opinion that collapse has been forestalled by avoiding the paroxysm of hypertension which normally occurs as these tumors are explored.

I would suggest, however, that use of C-7337 may be preferable to the drugs described by the speaker. Priscoline, for example, has some sympathomimetic actions. The hypotensive effect of Dibenamine is long-lasting, twenty-four to forty-eight hours, and is not reversible. It is better that a drug such as C-7337 be employed since its hypotensive effects disappear soon after operation is completed. Benzodioxane as described is used in small doses as an adrenolytic drug since in large or sympatholytic doses it is toxic. Its weak sympatholytic hypotensive action makes it a good testing drug.

I would suggest also that treatment of patients with adrenalin-secreting tumors be begun a few hours before operation using C-7337 in single or, if necessary, repeated intravenous injections of 1/12 to 1/6 mg. per kilogram. This will bring the blood pressure down to normal and let the patient recover from this major vasomotor adjustment. Then after two or three hours and after repeated injections of C-7337 if necessary, anesthetic and operation may be performed with the patient in good vasomotor equilibrium.

I want to caution that, as you know, false positive benzodioxane tests may occurs. To minimize chance of error we routinely use the benzodioxane test and, if positive, the

C-7337 test, and if that is positive, a blood adrenalin determination by Shingleton's method. We have encountered one false positive test in a man with uremia and proved absence of tumor by autopsy. In this particular uremic patient positive benzodioxane, positive C-7337, and positive blood adrenalin occurred without tumor. These drug tests are not specific for pheochromocytoma, rather they are specific for hypertension from circulating blood adrenalin.

Of the various drugs available, Dr. Console, Dr. Dunbar, and Dr. Ray have carefully studied most of them. Unfortunately they did not have access to C-7337. It is, however, now readily obtained. Testing or use in patients suspected of having pheochromocytoma should be done with very small doses. Ordinary patients will take 50 mg. total dose without difficulty. In the three with pheochromocytoma, however, 2 or 3 mg. per patient was all that they would tolerate and was enough to restore and maintain blood pressure to normal.

DR. M. RAVITCH.—Recently Dr. Robert Mason used benzodioxane preoperatively in a man with pheochromocytoma. The patient's pressure with histamine rose over 300 mg. of mercury. The rise was completely inhibited by the benzodioxane. Incidentally, the patient's tumor, as in a second case in which Dr. Scott participated, was demonstrated by the laminograms so that we knew on which side the tumor lay.

In our patient it was not necessary to use benzodioxane at operation. There was no rise in pressure during the procedure or subsequently, and it is probably of considerable importance to dissect out the vena cava in the transperitoneal approach and carefully attack all the tributaries coming from the tumor before manipulating the tumor at all.

ANASTOMOSIS OF THE CERVICAL ESOPHAGUS: EXPERIMENTAL EVALUATION OF PERITONEAL GRAFTS

I. Two-Layer Anastomosis

LeRoy J. Kleinsasser, M.D., Irving Cramer, M.D., and
Harold Warshaw, M.D., Dallas, Texas

(From the Department of Surgery, Veterans Administration Hospital, and Southwestern Medical College)

SAINT and Mann,[1] in 1929, stated the problems which make esophageal surgery more difficult than gastrointestinal surgery: (1) anatomic situation; (2) lack of a true serosa; (3) poor blood supply; (4) movement of the esophagus on respiration and deglutition; and (5) lack of omentum to protect and favor healing of suture lines.

They performed simple division and suture of the cervical esophagus in six dogs. There was slough of the suture line with ensuing infection in only one. They felt this was due to faulty technique, since the line of anastomosis was in the most vascular region of the cervical esophagus, the lower cervical esophagus. This was later repeated successfully in one dog. Four held in the least vascular regions, the upper and middle cervical esophagus. In addition, they successfully resected up to 4 cm. of the cervical esophagus in three of four dogs. It was emphasized that the esophagus does not possess a serous covering. By contrast, when intestine is sutured, the serosa throws out lymph which coagulates, thereby sealing the suture line rapidly.

They emphasized three important points necessary for the successful anastomosis of the esophagus: (1) interrupted suture to conserve the blood supply of the anastomosis; (2) sectioning of the left phrenic nerve to help immobilize the site of operation; and (3) prevention of intake and maintenance of nutrition intravenously to place the esophagus at physiologic rest.

Devine,[2] in 1946, reported the use of peritoneal grafts, covering a continuous single-layer through-and-through anastomosis of the divided colon in dogs. The graft was applied by five minutes' pressure over the suture line, using the plasma clot method. Only one developed soiling of the peritoneum, and this was through a hole in the graft. When no graft was used, fatal peritonitis resulted. Later, Chester, Bell, and McCorkle[3] reported the use of this same principle, suturing the graft into place. Gross and microscopic studies showed good healing.

It appeared desirable to employ the same principle in anastomosis of the esophagus. The cervical esophagus was chosen as it is a region with a rather limited blood supply, subjected to considerable tension and distention on deglutition as well as respiration, and is in a readily accessible area.

EXPERIMENTAL PROCEDURE

Eighteen mongrel dogs, with average nutrition, weighing about 30 pounds, were operated upon using intravenous Nembutal anesthesia. An incision was

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made in the midline of the neck extending inferiorly 5 cm. from the level of the cricoid cartilage. (In four animals a collar incision was made through the skin.) The trachea was exposed by separating the strap muscles. The esophagus was exposed to the left of the trachea, freeing the recurrent laryngeal nerve. The esophagus was dissected free and lifted from its bed. Several small arterial branches to the middle part of the cervical esophagus were divided, so as to free a 4 to 6 cm. segment of esophagus. In one-half of the animals, rubber-shod clamps were applied to the esophagus on either side of the proposed level of division. In the remainder, the operative site was merely walled off and sutures employed to prevent retraction of the cut ends of the esophagus.

Simple division of the esophagus was performed, followed by end-to-end anastomosis in two layers. In fourteen of the animals an end-to-end anastomosis was performed in a manner similar to that described by Saint and Mann. This consisted of an inner layer of interrupted No. 70 cotton sutures, placed through the entire thickness of the wall, the knots tied on the inside; no particular attempt was made to approximate the mucosa. A second layer of interrupted No. 70 cotton sutures was placed as an inverting row. These were intended to include only the muscularis.

Four additional end-to-end anastomoses were performed by removing a cuff of muscularis about 0.5 cm. wide from the promixal end of the cut esophagus, and a like cuff of mucosa and submucosa from the distal segment. A two-layer approximation was done by telescoping the remaining proximal mucosa and submucosa into the cuff of muscularis of the distal segment. This provided a two-layer anastomosis, with the suture lines at different levels.

Peritoneal grafts, 2 by 5 cm., were then taken from the abdomen through an upper midline incision from the region of the operative site. These were applied to the anastomotic line, with the serosal side in and fixed in place with several small interrupted No. 100 cotton sutures to both segments of the esophagus. These were applied in nine of the dogs. Thus there were nine two-layer anastomoses without a peritoneal graft and nine with a peritoneal graft.

The animals were sacrificed on the tenth to the twelfth days and bursting strengths of the anastomoses determined. The esophagus was resected about 6 cm. on each side of the anastomosis and the distal end clamped with a large hemostat. The proximal end was threaded on a glass tube and tied securely into place. This was connected to a mercury sphygmomanometer by means of a glass T tube. The entire specimen was immersed in water and inflated slowly, while one of us carefully watched for the escape of air from the suture line, and the other one watched the pressure scale. The pressure was recorded at the exact moment that the first bubble of air escaped from the suture line. The highest point on the pressure scale used was 260 mm. of mercury.

RESULTS

Of the nine anastomoses with a peritoneal graft, one dog was killed the first postoperative day due to the development of distemper, and one died the tenth day and was inadvertently discarded. Of the seven remaining dogs, two

developed disruption and leakage of the suture line, one on the fourth day and one on the third day.

Of the nine anastomoses without a peritoneal graft, one developed leakage of the suture line on the tenth day. The rest were intact and strong.

Thus there appeared to be no particular advantage to the use of peritoneal grafts in a two-layer anastomosis although the grafts became intimately adherent to the esophagus and microscopically were indistinguishable from the adventitia of the esophagus. In further evaluating the strength of the suture line as determined by bursting pressures, it was found that the readings recorded for the anastomoses with the peritoneal grafts varied from 10 mm. to 260 plus mm. of mercury, and those without the use of a graft varied from 20 mm. to 260 mm. of mercury. It was significant that the disruption always occurred at the suture line.

Of the sixteen dogs remaining after excluding two, one dying of distemper and the cause of death unknown in the other, thirteen remained intact, with a failure of healing in three (18 per cent).

The dogs were selected at random and given no special preoperative care. Intravenous fluids were given for twenty-four hours, after which the animals were allowed liquids by mouth, and a kennel diet was started on the third day.

COMMENT

In spite of the many statements made about the lack of serosa or a protective layer over the esophagus making surgery of the esophagus hazardous and difficult, it would appear that the application of peritoneal grafts to the suture line does not enhance the success of the anastomosis in a two-layer approximation in the cervical esophagus. Miller and Andrus[4] long ago emphasized the necessity of including the submucosa in the suture line. They found that if the lower one-third of an esophagus recently removed from a patient is divided and then joined by two layers of fine silk sutures, the artificial juncture withstands the pressure of a column of water 182.9 cm. (133½ mm. Hg) high. From this it is apparent that the esophageal wall has the required strength for suturing and that all the leakage and disruption occur subsequently. One factor is a relatively poor blood supply. Investigations of the blood supply of the esophagus in the dog by Saint and Mann, in a manner similar to that used by Demel in his work on the blood supply to the esophagus in human beings, demonstrated the blood supply to be segmental and anastomosis between segments scanty. The parts of the esophagus with the poorest blood supply are the middle and upper parts of the cervical segment and the lower thoracic segment. However, Parker and Brockington[5] concluded, on the basis of experimental observations in twenty-one dogs, that the arteries supplying the thoracic esophagus must have frequent anastomosis throughout. They reported survival of the esophagus following division of all the blood vessels to the esophagus except those entering the cervical and cardiac portions. They felt that the failure of healing was mostly due to tension. We are not prepared at this time to state with certainty the reasons for failure of healing in

our dogs. We feel that it is a combination of infection, tension, and interference of blood flow. We are now engaged in a series of experiments to elucidate these factors.

SUMMARY

Transection and two-layer end-to-end anastomosis was performed in eighteen dogs. Of sixteen studied, three developed leakage of the suture line, a failure of 18 per cent. One-half of the anastomoses were covered with peritoneal grafts. The grafts appeared to be of no benefit. Bursting strengths of the anastomotic lines were determined and showed no additional strength of the anastomoses with grafts. Emphasis is placed on a well-performed two-layer anastomosis, one layer of which must include the submucosa.

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DISCUSSION

DR. H. J. McCORKLE.—Since we were quoted in the reference, I should like to say a word in defense of peritoneal fascial graft. We have had considerable experience with this type of graft in experimental surgical work in anastomoses of dogs' intestines but very little in human surgery.

Certainly technical factors and the skill with which the anastomosis of the esophagus is done are most important factors in the success of anastomosis of the esophagus. Careful preservation of blood supply and the other factors mentioned by the author are very important. We believe that a single row of sutures is less likely to interfere with the blood supply of an anastomosis in the esophagus than multiple rows of sutures, and therefore we use only one carefully placed row of sutures.

It is conceivable that a double row of sutures may interfere with blood supply to small areas about the anastomosis and thus cause necrosis and leakage.

In unpublished experiments we have produced defects in the esophagus, in the wall of the stomach, and in other parts of the gastrointestinal tract. In the stomach, some of these defects have been as large as 2 cm. in diameter. We have closed these defects by placing a peritoneal fascial graft over the defect. I believe fifteen out of sixteen animals with stomach defects have survived; in these cases only the peritoneal fascial graft was used for closure.

We now place the fascial side of the graft toward the defect. This has two advantages; first, the graft seems to be more likely to take without leakage or breakdown, and second, it permits the serosal surface to present on the surface of the intestine, a desirable feature in abdominal procedures.

In the smaller esophageal defects there has been no leakage when they were closed with peritoneal fascial grafts.

In experimental surgery gastric resections have been done on dogs in which the duodenal stump has been inverted with only one or two plain fine catgut sutures—obviously insufficient reinforcement of the duodenal stump. In animals in which this inadequately sutured duodenal stump was reinforced with a peritoneal fascial graft, satisfactory healing was obtained.

DR. O. SWENSON.—We have been interested in the problem of how much tension a suture line of the esophagus can tolerate before a leak develops. In the course of operating upon eighty babies with esophageal atresia we have found we can bridge gaps of as much as 5 cm. with successful end-to-end anastomoses.

Two years ago, Dr. Clatworthy and I set out to determine how much of the dog's esophagus could be resected and end-to-end anastomosis performed. It was found in a series of dogs that 50 per cent of the thoracic esophagus could be resected and successful end-to-end anastomoses performed.

In a small number of patients resections of short lesions of the esophagus have been performed with end-to-end anastomoses. All our work on patients and in the laboratory indicates a two-layer anastomosis is far safer than a single layer.

DR. L. J. KLEINSASSER (Closing).—I agree with Dr. McCorkle that a one-layer anastomosis is effective. We are now doing this. I am unprepared to say what the final outcome will be because the control series is not completed. However, we have been doing one-layer anastomoses of the cervical esophagus in dogs, and it appears to be just as effective as a two-layer anastomosis. I cannot say positively, but it does not appear that the graft has helped.

Now it may be that the difference between the results is the fact that some sealing of the suture line occurs from the plasma clot method, and I assume he has utilized some modification of that procedure, whereas we have merely sutured the graft in place. It may be that it is during this period of time that some of the contamination occurs.

I want to emphasize the importance of infection. On examination of microscopic sections of the repaired esophagus, we note that there is a great deal of reaction around the suture line; much more reaction than one sees if penicillin is used in the postoperative period.

SURGICAL ASPECTS OF ABNORMAL TWINNING

JACK M. FARRIS, M.D.,* AND RICHARD C. BISHOP, M.D., LOS ANGELES, CALIF.

THE twin birth rate as reported by United States census is 11.5 per thousand—a value exceptionally stable in the statistical universe. Certain aberrations in the more subtle underlying growth mechanisms by which twin structure is established may result in pathologic enigmas which fall within the realm of surgical endeavor. The incidence of twinning, whether measured by the percentage of families with twins or by the ratio of twin births to total births, is similar and high consistently in families of patients with ovarian dermoids,† childhood teratomas,‡ and patients with twin pregnancies.[11] This evidence supports the theory of similarity of pathogenesis of teratomatous tumors and twins.

Abnormalities in the twinning process related to time of fission or relative proportions of divided segments are probable logical modifiers of a process which may result in teratologic fiascos, such as conjoined twins (equal and unequal). The lay public is well acquainted with the classic example in the "Siamese twins"—generally designating any type of conjoined twins—from such publicizing of a pair brought to this country from Siam.[31]

A point of interest in connection with such anomalous embryos in laboratory animals is the frequency with which they appear in the study of embryos obtained very early in development, as compared with a much smaller proportion at the close of embryonic life. This implies a heavy mortality during the developmental stage. In all probability a similar situation exists in man, and the small number of conjoined twins and other allied abnormalities born at full term is a result of intrauterine mortality followed by spontaneous abortion.[21]

Fig. 1, *A* illustrates a conventional classification of these equal and unequal conjoined anomalies in human beings—a rare accident in the development of monovular twins. Conjoined twins may be attached at three different levels[33]: upper, middle, and lower. They are named with a suffix *pagos* (Greek root = fastened) along with the appropriate anatomic term, so that head-to-head union is referred to as "craniopagus," chest-to-chest union "thoracopagus," and caudal union "pygopagus."

Surgical separation of such an arrangement is feasible when the degree of fusion constitutes a union of superficial tissues. However, in most instances separation is precluded by intimate interrelation of vital structures, such as heart, diaphragm, liver, and so on.

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*From the Department of Surgery, Moore-White Clinic.

†The term "dermoid" refers to a cystic tumor of the ovary which contains hair and sebaceous material, and may contain frequently additional structures as teeth, cartilage, and glandular tissue.

‡The term "teratoma" refers to a tumor which contains more than one tissue element; that is, nerve and muscle, hair and cartilage, etc. They are usually encountered along the spinal axis and are situated commonly in order of frequency in the pelvic, retroperitoneal, sacrococcygeal, and thoracic regions.

Fig. 2 illustrates a dissected specimen of a thoracopagus,[33] which indeed provides a predicament calling for prodigious as well as ingenious surgical maneuvers to affect separation. The sites of connection for unequal conjoined twins (Fig. 1, *B*) are the same as for the symmetrical ones. In this instance, for some reason or another, growth appears to lag in one, so that the less complete twin is referred to as "parasitic" and the host as an "autosite." Whereas

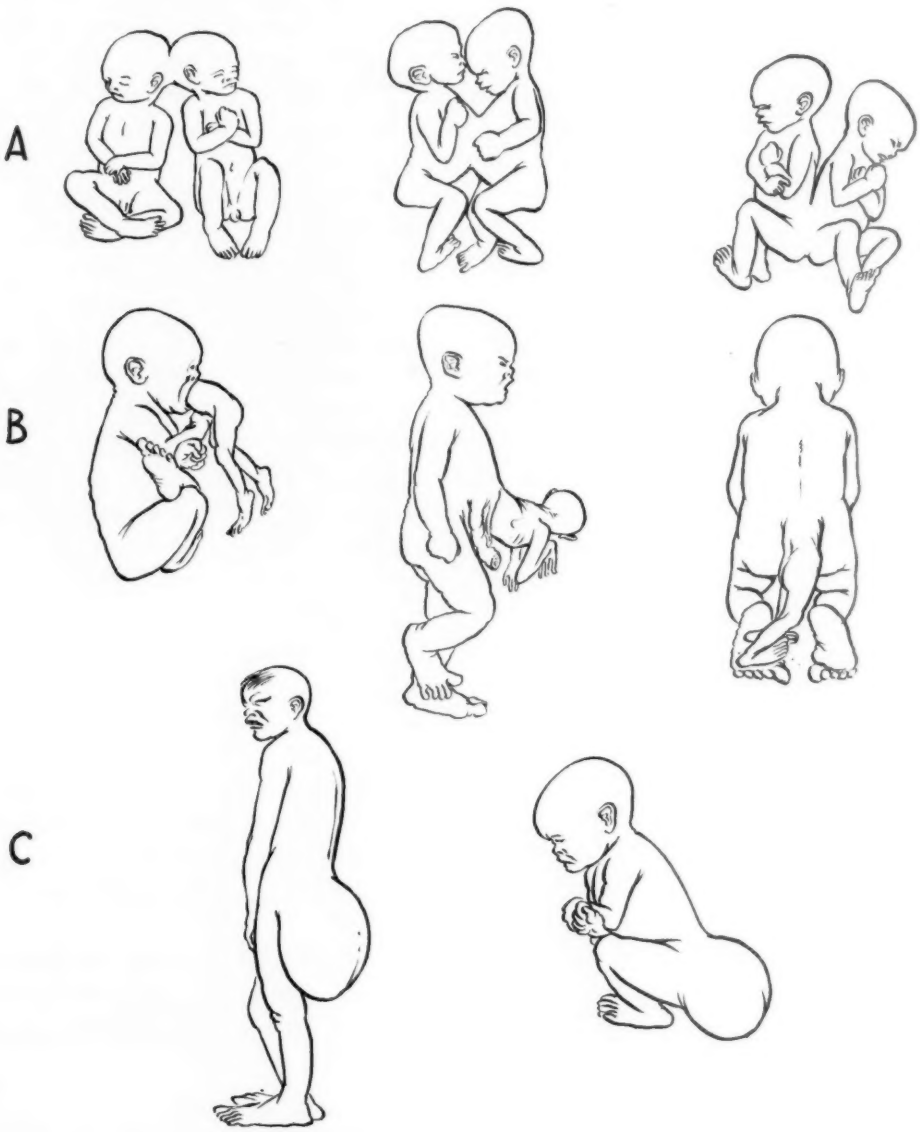


Fig. 1.—*A*, Diagrammatic representation of conjoined equal twins. From left to right: craniopagus, thoracopagus, and pygopagus. (From Patten.[31])

B, Illustrates conjoined unequal twins at upper, middle, and lower levels. The smaller twin in each instance is known as parasitic, and the host is referred to as the autosite.

C, Left figure: a 24-year-old farmer with a 31 pound sacrococcygeal teratoma containing rudimentary arm bones and a hand. (After Brines.[6]) Right figure: diagrammatic representation of sacrococcygeal tumor in an infant (a personal case operated upon at the University Hospital, Ann Arbor, Michigan).

conjoined equal twins may survive up to thirty-four years,[33] the unequal variety suffers from a high mortality. In either instance the twins are generally considered to be monovular.

A variation in the mechanisms by which conjoined structure is established may result in the so-called "included twin." Fig. 1, *C* represents examples of teratomatous tumors in the sacrococcygeal region, a classic location for a tumor containing well-developed organoid structures without the external morphologic characteristics of the human form. In the case of the adult with the large sacrococcygeal tumor, the interior was covered with thin white skin on which was growing long, black, curly hair. Protruding from the medial surface of the tumor into the large cavity was a definitely formed hand with

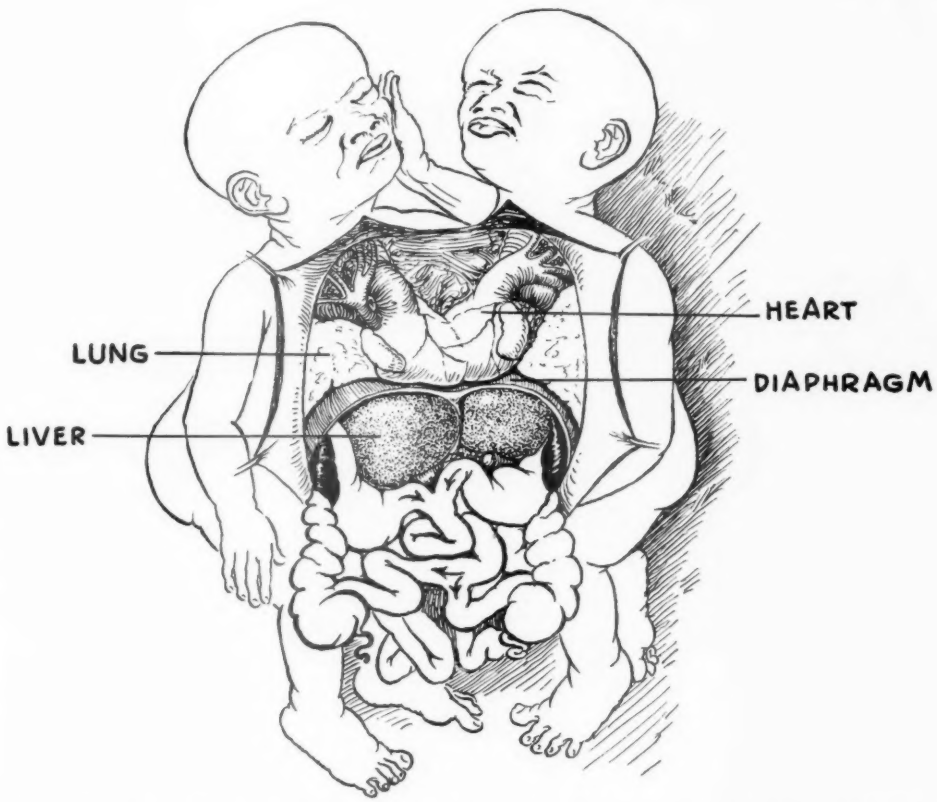


Fig. 2.—A diagrammatic representation of a thoracopagus with intimate relationship of heart, diaphragm, liver, and gastrointestinal tract. (Redrawn from Schwalbe.[33])

the palmar surface directed posteriorly. The thumb of the hand was about normal size and bore a small supernumerary digit. Study of this tumor as a whole together with a roentgenogram revealed clearly the fact that an extra upper extremity had developed quite a degree of perfection in this large teratoma. This tumor occurred in a Chinese farmer 24 years of age, and weighed 31 pounds.[6]

A fourth intermediate category of such conditions is represented by cases designated as included twins, where the parasitic component possesses

external morphologic characteristics of the human form. Such a condition (fetus in fetu) is believed to arise when a member of a conjoined twin early in development starts to lag behind and eventually becomes encased in the body of the more normal twin. A twin included within the abdominal cavity of the host is a rare anomaly.[12] A case of such a fetus recently observed serves for the following report.

CASE REPORT

Illness at Time of Admission.—A 4-month-old white female child was admitted to the California Hospital on April 5, 1949, because of an abdominal mass. This mass had been found upon a routine examination two days previously, and was epigastric in position. The child's previous history was normal essentially. There had been satisfactory weight gain and mental development, and there were no symptoms referable to the gastrointestinal tract. The child was born Dec. 6, 1948, following a full-term pregnancy with spontaneous delivery. Physical examination at that time was reported as normal.

Family History.—The family history was significant because of the following record of twinning in the family tree. Father's side: The paternal grandmother was a twin, and the maternal grandmother had twin brothers. A first cousin (maternal) had been operated upon for twin fallopian pregnancy, and another first cousin (paternal) had twin boys (fraternal). Mother's side: Paternal aunt had two sets of twins, and a maternal grandfather had twin sisters. The paternal great-grandmother was a twin, and the paternal great-grandfather had twin sisters.

Physical Examination.—The infant was a well-developed and well-nourished white female child weighing 13 pounds. The findings were normal except for the abdomen. In the midepigastrium there was a protuberant mass approximately 10 cm. in diameter which was slightly movable, firm, smooth, and nontender, without pulsation or thrill. It did not appear to move significantly with respiration.

Laboratory Data.—Urine was normal except for a trace of albumin and 2 to 3 erythrocytes per high power field. Hemoglobin was 11.25 Gm. per 100 c.c. (66 per cent), erythrocytes 3,580,000, color index .92, leucocytes 9,800, of which there were 49 per cent polymorphonuclear leucocytes, 47 per cent lymphocytes, 2 per cent monocytes, and 2 per cent eosinophiles. Roentgen examinations revealed a large tumor-mass in the left upper quadrant extending across the midline (Fig. 4). Multiple calcific deposits were noted within the tumor, suggesting poorly formed elements of a fetal skeleton. Subcutaneous pyelography was carried out and revealed poor filling of the left kidney. A barium enema showed no evidence of obstruction. The transverse colon was displaced inferiorly and anteriorly by the mass in the left upper quadrant.

Operation.—With a preoperative diagnosis of intra-abdominal teratoma, the patient was operated upon April 8, 1949. Ether anesthesia was given, an inlying cannula placed in the greater saphenous vein at the ankle, and a blood transfusion begun. A long transverse incision was made in the upper abdomen through the midepigastrium with division of both rectus muscles. A tremendous mass was encountered, occupying the entire upper abdomen (Fig. 3). The stomach was displaced superiorly and the colon inferiorly. The mass could not be visualized accurately, however, because it was beneath the gastrocolic omentum in the lesser peritoneal space.

Division of the gastrocolic ligament revealed a smooth, whitish, spherical tumor-mass occupying the entire lesser omental bursa. This mass was adherent firmly to the transverse mesocolon and blood supply, superior mesenteric vessels, head and body of the pancreas, and the posterior wall of the stomach. An initial attempt to remove the mass *in toto* was abandoned almost immediately because of its intimate attachment to vital visceral vascular patterns. Accordingly, the mass was opened with liberation of approximately 50 c.c. of straw-colored fluid in which floated particulate matter resembling vernix caseosa. A lower extremity of a fetus was recognizable because of the presence of rather well-developed digits. The entire fetus was then delivered, and a vestigial placenta could be visualized in the depths of

the wound, which was approximately 3 cm. in diameter and from the center of which protruded an umbilical cord. The placenta was adherent intimately near the origin of the superior mesenteric artery, and it appeared hazardous to attempt to dislodge its attachment. The upper one-half of the amniotic sac was excised, and the lower one-half along with the placenta was left intact. Two Penrose drains were placed in the region of the pancreas and brought out through the wound.

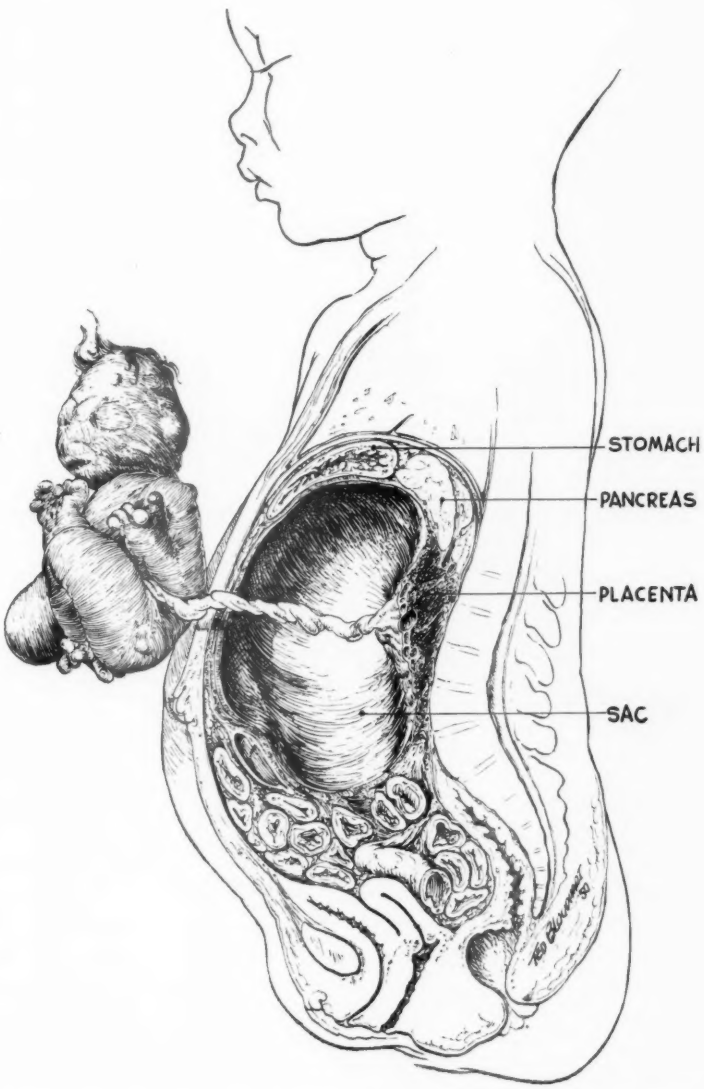


Fig. 3.—Schematic diagram illustrating anatomic relationship of included abdominal fetus within the lesser omental cavity. The stomach is displaced superiorly and the colon inferiorly. The remnant of the fetal membrane, which in this instance was left intact with formation of a pseudocyst, is shown.

During the operative procedure technical difficulties were encountered with the blood transfusion apparatus, and the condition of the infant at the conclusion of the procedure was alarming. She was exceedingly pale and showed signs of shock and respiratory depression. When the difficulties anent the transfusion were corrected and 50 c.c. of blood given rapidly with positive pressure, the condition of the patient improved considerably. Because of her poor condition the wound was closed rapidly, utilizing simple through-and-through interrupted sutures of black silk.

Postoperatively the patient was given the usual supportive measures, including penicillin and intermittent gastric lavage with carefully supervised feeding schedule. Fluid intake was maintained by the usual methods and the general course was satisfactory, allowing discharge on the fifteenth postoperative day. The sutures were left in place for seven days and produced moderately severe inflammatory reaction about them. The drains were removed on the eleventh postoperative day. Weight at the time of discharge was 12 pounds 2¼ ounces.

Fig. 4.—Preoperative roentgenogram showing large abdominal mass containing skeletal components, with displacement of gas-filled intestines inferiorly and to the right

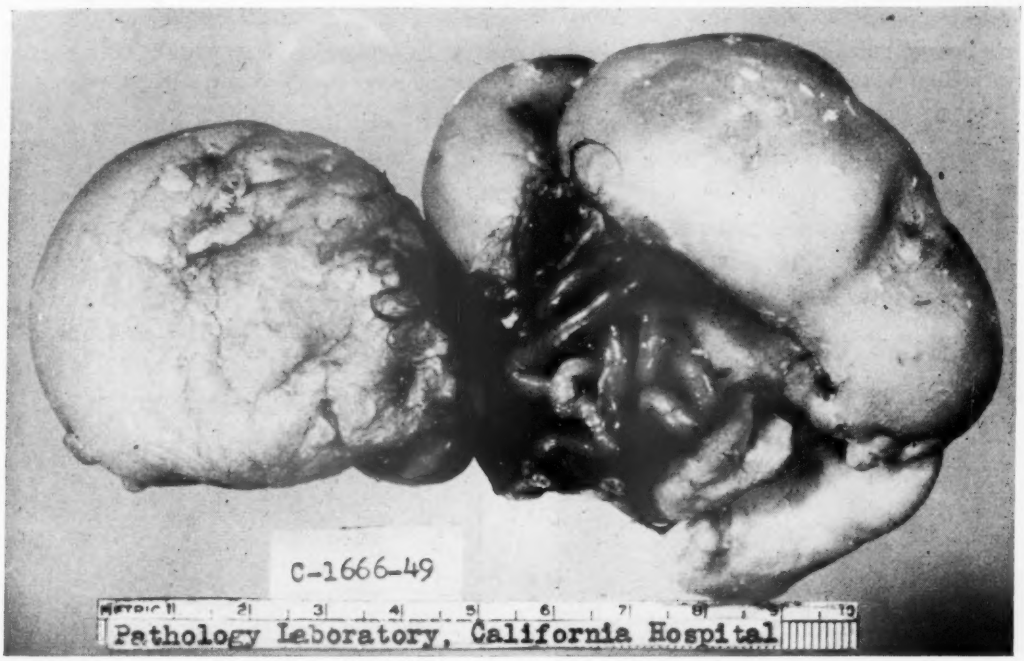
Pathology Report.—The gross specimen consisted of a fetal monster measuring 13 to 14 cm. in length. Extremities were present and were developed poorly (Fig. 5).

Head: The head was malformed but showed two concentric depressions 1 cm. in diameter, presumed to be optic cups. There was definite bone at the base of the skull, where there was a 6 mm. indentation which could be probed for a distance of 5 mm. and represented probably the foramen magnum. There was a small amount of hair distributed near the base of the head.

Extremities: The upper extremities each contained two digits and were flexed at the elbow. The lower extremity (left) possessed four digits with nail-beds and nails. These digits were large disproportionately and measured 6 cm. in greatest dimension. The right foot had four digits. Both feet had well-developed plantar and dorsal surfaces, and each contained long bones resembling metatarsals and phalanges.

Abdomen: There was an omphalocele with protrusion of the entire intestinal tract, containing a stomach which appeared to end blindly at the diaphragm and represented possibly a diaphragmatic hernia. A definite heart could not be demonstrated. There was a complete small intestine with an apparent ileocecal differentiation. The colon ended in a well-

developed anus at the base of a 7 mm. tuft, and was patent. There was no suggestion of a penis. The perineum showed signs of poorly developed external genitalia. There was a perineal body and suggestive labia majora. Differentiation between male and female was not possible. There appeared to be a column of bone down the midline posteriorly.



A.

B.

Fig. 5.—*A*, Parasitic fetus removed from the lesser omental bursa covered with normal-appearing piliferous skin. There is a well-developed gastrointestinal tract and four imperfectly developed extremities.

B, Roentgenogram of operative specimen, showing skeletal components. Note well-developed digits.

Subsequent Course.—Following operation there were intermittent attacks of vomiting associated with occasional elevation of temperature to 101° F. A residual mass could be palpated in the abdomen. The weight on Aug. 15, 1949 (four months postoperatively), was 17 pounds. Examination showed a well-developed 8-month-old child. There was a non-tender smooth mass in the left upper quadrant extending about 5 cm. below the lower costal margin. Ordinary roentgenogram revealed soft-tissue density in the upper abdomen, obscuring both kidney and psoas shadows, with moderate displacement of the normal intestinal pattern (Fig. 6). Intravenous pyelograms showed no abnormalities.

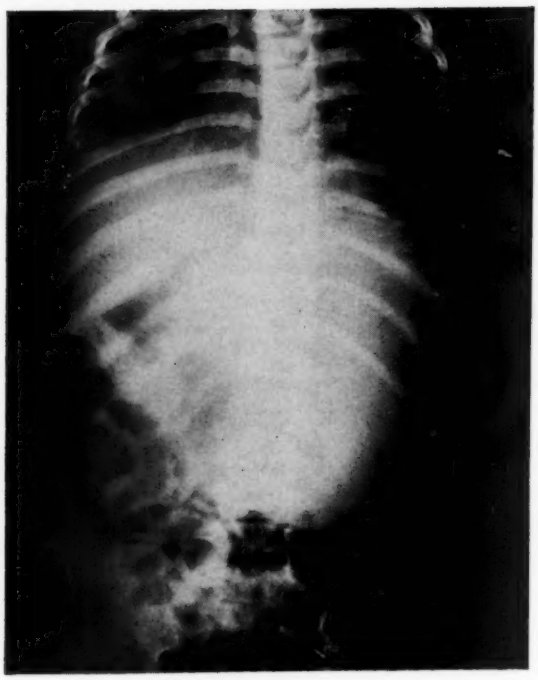


Fig. 6.

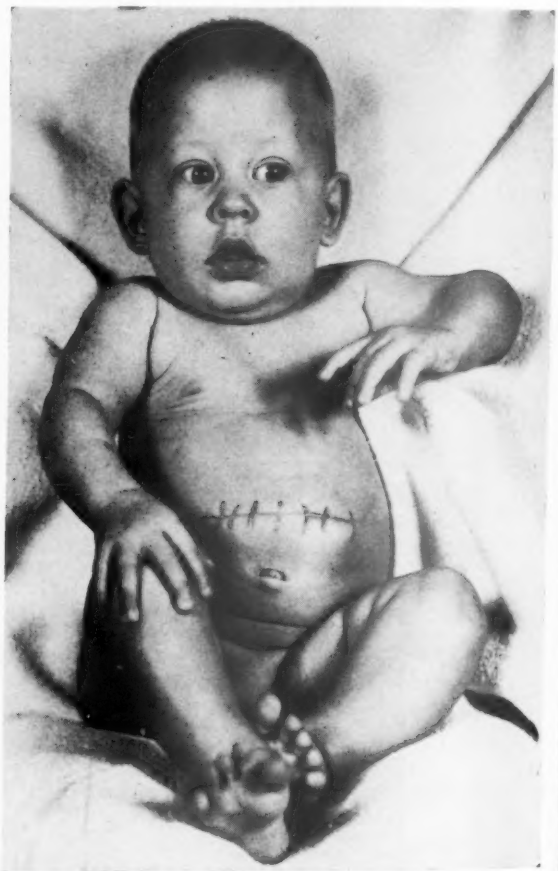


Fig. 7.

Fig. 6.—Postoperative roentgenogram taken four months after surgery, showing large pseudocyst of the lesser omental space. This cyst did not interfere with the progress of a motor barium meal. Recent examinations show it to be approximately one-third of this size.

Fig. 7.—Host infant at the age of 5½ months. There is normal physical and mental development.

At the present time the patient is now 14 months postoperative and shows excellent physical and mental development (Fig. 7). The abdominal mass is disappearing gradually. Recent upper gastrointestinal x-ray studies showed a normal gastric and duodenal pattern with excellent progress of the motor meal through the entire gastrointestinal tract. A small hernia which appeared at the site of drainage in the wound early in the convalescence is no longer apparent.

Comment.—From the surgical viewpoint one or two aspects are worthy of comment. The case reported here presented technical problems in that removal of the amniotic sac and placenta was impossible because of intimate

association with the visceral circulation. There was no alternative to leaving the fetal membranes in place. The abdominal mass which developed after operation undoubtedly represents a pseudocyst, which in this case has disappeared gradually under a conservative regimen. Obstetricians who operate for ectopic intra-abdominal pregnancy find an analogous situation. In this event it is commonplace to make no attempt to remove the placenta and little difficulty results.

A complete review of the English literature failed to reveal a parasitic fetal inclusion within the abdominal cavity with such well-developed external morphologic characteristics.[2-4, 8-9, 13, 16-19, 22-25, 27-30, 32, 34-35, 37] Ballantyne[4] described a case of an amorphous fetus removed from the lesser peritoneal cavity of a female child 2 months of age. It contained much adipose tissue, pieces of cartilage, and membrane-lined cavities. Dermoid cysts and teratomas within the abdominal cavity and retroperitoneal areas are not so rare, but none of those reported in the literature approached the development of the case reported here.

Harrington[15] reported a rather well-developed fetal parasite within the anterior mediastinum containing four bud-like outgrowths resembling extremities. There were well-developed organoid structures, including pancreas with island of Langerhans.

Ewing[12] stated that Lexer[21] reported seventeen cases of definite fetal implantation in the abdomen. Their location was in the transverse mesocolon or behind the liver and the lesser omental bursa with a vascular supply from the aorta or its branches. The subjects were from a few days to 61 years of age.

Kimmell and associates[20] have reported recently a case of intracerebral inclusion of multiple human fetuses. A hydrocephalic female died nineteen days after delivery. Autopsy revealed a tumor replacing the parietal and occipital regions of the cerebrum. The mass contained five fetuses; two were distinct individuals and three were identifiable by extremities.

The family history of twinning in the case reported is significant. Twin production in certain families is three times more frequent than in the general population.* This proportion refers generally to biovular twins. Whether or not there is a similar tendency in the production of single-egg identical twins is disputed.[1] Cumulative data of Edmonds and Hawkins[11] indicate a high incidence of twinning in the families of patients with ovarian dermoids and in the families of patients with childhood teratoma, similar to the high incidence and rate of twinning in the families of mothers giving birth to twins. Inferential alternative mechanisms may explain the oncogenesis of these conditions. It seems most likely that the process involves a splitting of the zygote with developmental separation of component proportions. Whether identical or fraternal twins are produced by similar mechanisms is an unsettled question. Curtins and von Verschuer[7] believe the mechanisms are similar. Most other investigators believe they are dissimilar.

*Guzzoni[14] is quoted by DeLee as having studied 50,000,000 births in which he found the ratio of twins to be once in 87 cases; triplets once in 7,103; quadruplets once in 757,000; quintuplets once in 41,600,000 births. About 30 instances of quintuplet births have been reported, but the first in which all five infants have survived more than a few days of life is the one of the now-famous Dionne quintuplets of Callander, Ontario.

One explanation of these anomalies attributes them to abortive parthenogenesis.[11] This theory implies a spontaneous development of ova or sperm cells without fertilization, a view supported by the fact that gonads are common sites for teratomatous tumors. In addition, teratomas of testes in the rooster may be produced by injections of zinc chloride,[26] and finally, teratomas in frogs may be produced by mechanical stimulation of eggs with reimplantation into the mother's body.[5]

The other mechanism concerns isolation and inclusion of a blastomere.[11] The primitive blastomere with its multipotency is thought to be capable of producing any of the various gradations of twinning abnormalities. The fact that teratomas occur in newborn infants lends credence to this theory. The fact that teratomas and twins appear to occur in the same families suggests a relationship with early division and inclusion of a blastomere.

SUMMARY AND CONCLUSIONS

A general review of some of the surgical aspects of abnormal twinning is presented. The relative frequency with which such anomalies occur in large groups of embryos early in development, as compared with a much smaller proportion appearing at the close of embryonic life, suggests that the apparent incidence of this condition in human beings is reduced by intrauterine mortality and spontaneous abortion. The high incidence of multiple births, teratomas, and dermoid cysts of the ovary in certain families lends support to the view that there is a related mechanism. A case is reported in detail of an included abdominal fetus (fetus in fetu) in a 4-month-old child with successful removal.

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Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS, FEB. 9-11, 1950, PHILADELPHIA, PA.

F. A. SIMEONE, M.D., BOSTON, MASS.

THE eleventh annual meeting of the Society of University Surgeons was held in Philadelphia, Pa., on Feb. 9, 10, and 11, 1950. The Department of Surgery of the University of Pennsylvania School of Medicine was host to the Society. The scientific program was presented in the auditorium of the University Museum.

On the first day of the meeting, **Dr. I. S. Ravdin** and **Dr. R. C. Buerki** welcomed the Society to Philadelphia for the University and papers were presented by members of the faculty of the University of Pennsylvania. Brief abstracts of the papers are included in this section. In the afternoon, a conducted tour of the Harrison Research Laboratories of the Department of Surgery was held.

On the second and third days of the meeting, papers were presented by members of the Society. In addition to those published in this issue of the JOURNAL, the following papers were presented:

The Dynamics of the Coagulation, J. G. Allen, and (by invitation) **P. V. Moulder,** and **D. M. Emerson.**

Indications for Surgical Treatment of Ulcerative Colitis With Special Reference to Nutritional State, R. T. Tidrick, M. E. Barrent, and **N. A. Womack.**

Complications of Decubitus Ulcers in Patients With Paraplegia, H. Conway.

Experiences With Pressure Sores in Paraplegia, B. Cannon (read by title).

At the annual dinner of the Society, **Dr. S. W. Moore** delivered his Presidential Address, which is published as the first article in this issue of the JOURNAL.

Abstracts of the papers presented by the faculty of the University of Pennsylvania, Feb. 9, 1950, follow.

Observations on the Lipotrophic Effect of an Extract of Pancreas, Jonathan E. Rhoads, Samuel Fox, Oscar Liboro, Thomas E. Machella, and **Paul Gyorgy,** Department of Surgery, Medicine, and Pediatrics, School of Medicine.—A new pancreatic extract (Sharpe & Dohme A 1) was tested in depancreatized dogs maintained on lard, casein, dextrose, vitamins, and salt. Liver biopsies were done after three to four weeks on the diet. The mean value for lipids in the unoperated dog was 4 per cent; for the depancreatized untreated dogs, 18.7 per cent; for the depancreatized dog treated with the extract, 8.0 per cent; and, for the depancreatized dog treated with extract that had been boiled for three minutes, 15 per cent.

The extract appeared to be active but the loss of its activity on boiling three minutes suggested that it might be an enzyme.

Factors Affecting the Distribution of Metastases; Experiments With Transplantable Tumors in Rabbits, Rats, and Mice, Dale R. Coman, Department of Pathology, School of Medicine.—The purpose of these experiments was to determine whether the "soil" afforded by different parts of the body plays a major part in the distribution of metastases, or whether this depends chiefly upon the availability of emboli. Injections of V_2 carcinoma cells into the left ventricles of rabbits resulted in tumors throughout the body, indicating no unfavorable "soil" factors. Using four transplantable tumors in three species, it was found that, in general, tumor implants grew equally well in muscle, spleen, liver, kidney, and adrenal. It is concluded that availability of emboli is the major factor in the distribution of metastases.

Relative Effectiveness of Bland Cake Soap, Liquid Soap With G-11, and pHisoderm G-11 for Preparation of the Surgeon's Hands, Harold Zintel, James Dull, H. L. Ellis, and **A. Nichols,** Harrison Department of Surgical Research.—With the use of a ten-minute cake soap scrub, the postscrub bacterial count was 28 per cent and the postoperative count was 79 per cent of the prescrub count. The postscrub count with a three-minute technique using pHisoderm G-11 was 26 per cent, and the postoperative count was 15 per cent. When liquid soap G-11 was used for three minutes, the postoperative count was 39 per cent. When pHisoderm G-11 was used for one week the resident flora was reduced 66 per cent and the postoperative count was 2.4 per cent of the original prescrub count. pHisoderm G-11 was superior to the liquid soap G-11 and both G-11 products were more effective in three minutes than cake soap was in ten minutes.

Studies on the Formation of Intraperitoneal Adhesions, John W. Thomas and **Jonathan E. Rhoads,** Harrison Department of Surgical Research.—In studies on the prevention of adhesions performed in rats and guinea pigs, effective controls were established by the use of surgical talc, 3 per cent sodium hydroxide, and by crushing bowel with selected surgical instruments.

Heparin and hyaluronidase were ineffective in preventing adhesions.

Oversewing superficially denuded bowel caused adhesions in 79 per cent, against 31 per cent when the area was not oversewn.

Insertion of methyl methacrylate (Lucite) abdominal windows allowed observation of adhesion formation from the time of injury to complete formation.

Studies of Oxygen Tension in Skin, Robert B. Brown and **Thomas J. Coleman,** Department of Surgery, School of Medicine, United States Naval Hospital, Philadelphia.—This investigation covers but one phase of a wider project involving the determination of oxygen tension in skin by the platinum electrode method. Its purpose was to determine whether artificially sustained increases in oxygen tension in fresh, excised skin would prolong its "life span" as measured by the total period of oxygen utilization. Studies were carried on at room temperatures and the small squares of full-thickness skin were immersed in sterile physiologic saline solution containing penicillin. Oxygen tension in the skin was increased by bubbling 100 per cent oxygen through the saline bath. Increase of oxygen tension in the skin under the experimental conditions as outlined did not produce any demonstrable prolongation of its "life span."

Endotracheal Anesthesia in Infants and Children, James Eckenhoff, Department of Anesthesiology, School of Medicine.—In infants and children anesthesia is best administered by the endotracheal route because it overcomes excessive dead space, provides a persistently patent airway, helps prevent an increase of the temperature of respired gases. A period of fifteen to twenty minutes must be allowed for the induction of anesthesia and the lungs should be flushed with oxygen immediately prior to tracheal intubation which is best accomplished under direct vision. The endotracheal tubes and equipment must be surgically clean to prevent laryngeal edema. The semiclosed technique is the best technique of administering anesthesia in the child of less than 5 years of age. In a two-year period at the Children's Hospital of Philadelphia, 96 per cent of 4,109 anesthesias were general, of which 1,147 were by the endotracheal technique. Six of these patients developed laryngeal edema, none requiring tracheotomy.

Life Cycle of the Spirochete, Edward D. DeLamater, Department of Dermatology and Syphilology, School of Medicine.—Evidence for the occurrence of a life cycle in pathogenic *Spirochaeta pallida* as observed by means of phase contrast microscopy was presented with extensive photographs. A brief summary of the historical aspects of the subjects supporting such a life cycle was also presented. It appears that there are two methods of vegetative reproduction of the *S. pallida* in related forms which consist of (a) transverse

division, and (b) the formation of gemmae or buds. The buds undergo differentiation into unispirochetal cysts. There is also evidence of the occurrence of very large multispirochetal cysts which apparently have two modes of origination, which are (a) following aggregation of two or more spirochetal forms with the production of such cysts at points of contact, and (b) by development and differentiation from within the body of a single spirochete. Further studies are planned which will elaborate the details of such processes.

Mechanism of the Dumping Syndrome, Thomas E. Machella, Department of Medicine (Gastrointestinal Section), School of Medicine.—Observations on postgastrectomy patients manifesting the ''dumping'' syndrome revealed that the symptoms occurred during, toward the end of, or immediately after a mixed meal. The symptoms were accompanied by a rise in blood pressure and an increase in pulse rate but not by hypoglycemia. The patients included individuals subjected to Hofmeister as well as the Pólya procedure. The ''dumping'' syndrome was reproduced in individuals with intact gastrointestinal tracts by balloon distention of, or by instillation of hypertonic solutions into, the jejunum. It is proposed that the ''dumping'' symptoms occur as a result of distention of the jejunum by excessive intestinal secretion induced by the presence in the bowel of a hypertonic solution. Most satisfactory plan of treatment consists of the omission of fluids from meals.

The Fate of Intravenously Injected Albumin, Nicholas Gimbel and **Cecilia Riegel,** Harrison Department of Surgical Research.—When human serum albumin is administered intravenously to healthy volunteers as the sole source of protein, positive nitrogen balance is immediately achieved. After two weeks, enough of the albumin is being catabolized so that nitrogen equilibrium comes about. Large amounts accumulate in the plasma and interstitial fluid, and, on intakes of 75 Gm. a day, congestive heart failure may develop within a week. Positive potassium balance suggests that some of the albumin has been incorporated into cellular protoplasm, but the cardiovascular side-effects alone are sufficient to make albumin an unsatisfactory agent for treating a general body protein deficit. Its chief usefulness is in replacing albumin deficits in the plasma and interstitial fluid.

Some Effects of High Partial Pressure of Oxygen on Man, C. J. Lambertsen, D. Y. Cooper, G. L. Emmel, H. H. Loeschcke, R. H. Kough, and **C. F. Schmidt,** Department of Pharmacology, School of Medicine.—In an attempt to chemically inactivate hemoglobin and prevent its reduction during passage through the brain, human subjects inhaled 100 per cent oxygen at 3.5 atmospheres in a positive pressure chamber. Prior to the onset of convulsions normally produced by oxygen at high partial pressure, samples of arterial and internal jugular blood were collected and the rates of cerebral blood flow and cerebral oxygen consumption were measured. High partial pressures of oxygen produced an increase in brain tissue pCO_2 and, hence, a stimulation of respiration, a decrease in arterial pCO_2 and a decrease in cerebral blood flow. Cerebral oxygen metabolism was unchanged.

Suture Methods and Arterial Growth, Julian Johnson and **Charles K. Kirby,** Harrison Department of Surgical Research.—The abdominal aorta was divided and resutured by four different methods in eight pigs weighing about 25 pounds. The animals were sacrificed at about 200 pounds. When the continuous everting mattress suture of silk was used, there was constriction at the site of anastomosis and dilatation beyond it. When a continuous over-and-over (Carrel) suture of silk was used, there was no constriction, probably due to the fact that both of these sutures were broken and the ends separated. When interrupted vertical mattress sutures of silk were used, there was an apparently perfect result. When continuous over-and-over catgut sutures were used, there was an apparently perfect result.

Heterotransplantation of Tumors in Chick Embryos, Doris Bender Maxwell, Harrison Department of Surgical Research.—The growths of heterologous animal tumors transferred to the chick chorioallantoic membrane, inoculated intravenously or into the yolk sac, were often profuse with 75 per cent ''takes'' and serial transfers easily effected.

Malignant human tumors were grown both by intravenous inoculation and transfer to the chorioallantoic membrane. Thin slices of human tumors grew more readily on the chorioallantois than minced tumor tissue. Percentage of "takes" of human breast carcinoma appeared to be increased by the addition of small amounts of aqueous estrogen or chorionic gonadotropin. Human tumor growth was small and serial transfer was not effected.

Transthoracic Repair of Diaphragmatic Hernia in Infants, C. Everett Koop and **Julian Johnson,** Department of Surgery, School of Medicine, and the Children's Hospital of Philadelphia.—A congenital diaphragmatic hernia producing symptoms in the newborn period should be dealt with as a surgical emergency. The difficulties of an abdominal approach to the repair of such defects can usually be eliminated by the transthoracic route. In a cyanotic, distressed infant, when chest is opened the viscera deliver themselves, the mediastinum is free to return toward the midline, the compressed lung can be expanded, and the patient becomes a relatively normal cardiovascular risk under anesthesia.

Twelve congenital diaphragmatic defects have been repaired transthoracically in infancy with two deaths, both from additional lesions incompatible with life.

The Correction of Electrolyte Deficits in Surgical Patients, James M. Walker and **Brooke Roberts,** Harrison Department of Surgical Research.—The care of surgical patients losing large volumes of secretions through intestinal intubation or fistulas necessitates accurate estimation of electrolyte and water deficits. Determination of these deficits is made from measurement of (1) blood volume (Evans blue dye), (2) extracellular fluid (thiocyanate), and (3) volume and electrolyte content of drainage and urine.

Electrolyte solutions found useful are 2 per cent sodium chloride, 2 per cent ammonium chloride, and 0.6 per cent potassium chloride in 0.45 per cent sodium chloride.

The debilitated patient with increased extracellular fluid and lowered electrolyte content will frequently excrete administered physiologic saline, but when given 2 per cent sodium chloride will usually excrete water nad retain some of the salt required.

The alkalotic patients responded most readily to solutions of potassium and ammonium chlorides.

The D_2O Dilution Space as a Measure of Total Body Water and the Relation of Body Water to Body Size, James D. Hardy and **David L. Drabkin,** Harrison Department of Surgical Research and Department of Physiological Chemistry, Graduate School of Medicine.—Total body water was measured with D_2O (heavy water). The "extracellular" and plasma spaces were determined with sodium thiocyanate and the dye, T 1824.

Six healthy men and four healthy women representing extremes and intermediates of leanness and obesity were studied. The leanest man had a value of 73 per cent of body weight as total body water and the fattest man only 43 per cent. The women presented similar values.

Conclusions.—(1) Total body water and body mass bear an inverse relationship to each other. (2) In adults of the same height, the difference in weight is largely due to difference in fat content. (3) The figure of 70 per cent commonly employed for total body water applies only in the abnormally lean subject. (4) Plasma volume and extracellular fluid may also have an inverse relationship to body fat.

Liver Regeneration, Harry M. Vars and **Otto Rosenthal,** Harrison Department of Surgical Research.—Liver protein regeneration is being studied in standardized rats after a 70 per cent hepatectomy. The amount of regeneration, in a stated period, was greatly affected by the type and amount of protein fed, and the total caloric intake. It was decreased after adrenalectomy, and was restored by adequate replacement therapy. It was not impeded in early common duct obstruction. Protein depletion increased the suscepti-

bility of the liver remnant to necrosis from noxious stimuli, for example, gastric distention and impaired circulation. Enzyme studies are giving information on the functional capability of the regenerating hepatic tissue.

Electro-Icono-Grams From the Cerebral Cortex (Cats and Monkeys at the Pial Surface): "Spontaneous" Activity and Responses to End Organ Stimuli Under Anesthesia, John C. Lilly, E. R. Johnson Foundation for Medical Physics.—A new technique and some of the results of its use are described briefly. The Bavatron* records some two-dimensional cross sections of the three-dimensional electrical activity of the brain (electro-icono-grams). The input field is picked up by twenty-five electrodes in a 5 by 5 square array (8 mm. by 8 mm.) on the pia, is amplified by twenty-five amplifiers, and used to intensity-modulate twenty-five light sources in a 5 by 5 square array at the output. The moving and fixed figures and forms of the electrical input field are thus transformed into corresponding patterns of variation of luminosity of the output field. The output field is photographed with a motion picture camera at 128 frames per second to obtain the records called electro-icono-grams or E.I.G.s.

By projecting the E.I.G.s at 16 frames per second on a screen subtending a visual angle of 0.1° to 1.0°, the following results can be seen by the observer: (1) In deep barbiturate anesthesia, the cortical responses to normal end organ stimuli can be seen to spread in the primary afferent areas in a stereotyped fashion from the zone first activated. (2) "Barbiturate waves" are seen to be simple forms which travel or which "grow" around a focus and fade away in place. (3) Spontaneous activity in the conscious animal has traveling, shifting figures of various velocities, sizes, and forms, depending grossly on previous stimuli.

Antibiotics in the Prevention of Death Following Ligation of the Hepatic Artery in Dogs, William T. Fitts, Jr., Russell Scott, and **J. A. Mackie,** Harrison Department of Surgical Research.—The recent work of Markowitz showing that penicillin prevents death following ligation of the dog's hepatic artery was confirmed and additional experiments using aureomycin and streptomycin were reported. Aureomycin was as effective as penicillin in preventing death, but streptomycin salvaged only one-third of the dogs. Control dogs, given no antibiotics, died within forty-eight hours with massive hepatic necrosis and peritonitis. The present experiments were not conclusive in determining how the antibiotics exerted their protective action.

The Polysaccharide and Huggins Tests in the Diagnosis of Cancer, Cecilia Riegel, Ralph Jones, and **Kenneth Welch,** Harrison Department of Surgical Research and the Department of Medicine, School of Medicine.—A study of the Huggins and the Seibert tests for cancer on the same sera indicates that (1) in 100 normal patients, in 50 patients with nonmalignant disease, and in 100 patients with carcinoma, the mean values for the three groups are significantly different; (2) there is considerable overlapping of individual values in the three groups; (3) the percentage accuracy of diagnosis in 100 cases of proved malignancy was for the Huggins test 53 per cent, for the Seibert test 66 per cent, each test being considered individually, and 77 per cent when the two tests were used together.

Renal Function in Coarctation of the Aorta, Harold G. Barker, John K. Clark, and **Archer P. Crosley, Jr.,** Harrison Department of Surgical Research and the Department of Medicine, School of Medicine.—Renal hemodynamic measurement (CPAH, CM, TmPAH) have been made in twelve patients with coarctation of the aorta and compared with normal mean values. In addition, eight of these patients have been studied after surgical correction of the coarctation, thus enabling each patient to serve as his own control for statistical analysis. Significant depression of CPAH existed in the twelve unoperated

*A.I.E.E.—I.R.E. Symposium Volume on Instrumentation in Medicine and Nucleonics, published by the American Institute of Electrical Engineers, April, 1950.

patients as a group and there was a significant rise with operation. CM was normal preoperatively and remained so after surgery. Filtration fraction was high preoperatively and remained so. TmPAH was normal preoperatively but rose significantly after operation.

An Instrument for the Detection of Gallstones in the Bile Ducts, Charles K. Kirby, Harrison Department of Surgical Research.—The problem of unremoved stones following exploration of the bile ducts is principally a problem of detection. The reported incidence of unremoved stones reflects the inadequacy of current methods of detection. A new instrument to aid in detecting gallstones during operation has been devised. It is an electroacoustic device which makes audible the contrast between the contact of a metal probe with a gallstone and with normal tissue. The instrument has been used during exploration of the bile ducts in 123 patients. In twelve patients stones were detected which, without the use of the instrument, would probably not have been removed.

Cerebral Circulation in Man, Seymour Kety, Department of Physiology and Pharmacology, Graduate School of Medicine.—Cerebral blood flow has been measured for the first time in man by examination of the concentrations of an inert gas (nitrous oxide) in arterial and cerebral venous blood. The mean value obtained in healthy young men is 54 $\pm$ 12 ml. of blood per 100 Gm. of brain per minute corresponding to a total flow of 750 ml. per minute for the whole brain. Studies have been made indicating a progressive decrease in cerebral circulation with increasing intracranial pressure. In essential hypertension cerebral blood flow is normal as the result of a marked increase in cerebrovascular resistance. Upon acute reduction of blood pressure in these patients, this resistance relaxes and cerebral blood flow tends to remain within the normal range.

Book Reviews

Atlas of Peripheral Nerve Injuries. By William P. Lyons, Ph.D., Associate Professor of Anatomy, University of California Medical School, and Barnes Woodhall, M.D., Professor of Neurosurgery, Duke Medical School, Durham, N. C. Philadelphia, 1949, W. B. Saunders Company.

This is mostly a series of photographs of pathologic material obtained from patients operated upon at the Walter Reed and Halloran Hospitals for various types of nerve injury. Approximately 1,000 such operations for peripheral nerve injuries were carried out, that is, about one out of every thirteen peripheral nerve operations performed during World War II in the zone of the interior. The gross specimens were obtained directly from the operating room and prepared for this study. A few specimens of early nerve suture and nerve grafts were obtained from other sources.

There is some clinical discussion and a few of the reported cases have follow-up data on the ultimate results of nerve suture. It is unfortunate that more clinical records of the end results as related to the pathologic conditions in the resected specimens are not included, but it is at least inferred that a later report will be made correlating ultimate functional recovery with the condition found at the time of repair.

Each chapter or section consists of a short discussion of the subject in general and this is followed by many illustrations of specimens to illustrate this subject. The principal headings of these sections are peripheral nerve structure, completely severed nerves, traumatic nerve lesions in continuity, nerve sutures, and nerve grafts, and these major topics are further subdivided into a variety of subtopics such as the histologic changes in the proximal and distal stumps, foreign body inclusions, traction lesions of nerves, associated nerve and vascular lesions, temporary coaptation, disruptured suture sites, reactions to suture material and wrappers, suture site neuromas, and others. Most specimens are profusely illustrated as gross longitudinal sections of the nerve, cross sections of the mirror images of the sutured ends, and multiple longitudinal and transverse microscopic sections of the resected specimen. It is stated that there are three well-defined factors that influence adversely the normal course of nerve regeneration, namely, (1) time interval between injury and definitive repair, (2) intrinsic neuropathology, and (3) extrinsic pathology. Suture two to three weeks after injury is advocated. It is amply illustrated that there is a progressive degeneration in the distal nerve segment with progressive shrinking of the axone sheaths and intraneural fibrosis. Many specimens to illustrate the unfavorable affect of nerve wrappers upon the sutured nerves are included.

A critical review of nerve grafting and the possibilities of success by this method is presented. In this atlas an abundance of material, much of it repetitious, is reviewed and illustrated, but it gives the neurosurgeon a concept of the condition of the injured nerve that he will not gain from the occasional case of nerve injury encountered in civilian practice. All surgeons who repair nerve injuries should be familiar with the material in this book.